DORSOLATERAL PREFRONTAL CORTEX AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA MRI VOLUMETRIC AND NEUROPSYCHOLOGICAL FINDINGS

By

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To my parents.

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DORSOLATERAL PREFRONTAL CORTEX AND THE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: MRI VOLUMETRIC AND NEUROPSYCHOLOGICAL FINDINGS

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Functional imaging and neuropsychological studies have implicated the dorsolateral prefrontal cortex (DLPFC) as a possible site of neuropathology in schizophrenia. We examined the relationship between negative symptoms of schizophrenia and the structural and functional integrity of a sub-region (Walker's area 46) within the DLPFC. Magnetic resonance images of 23 schizophrenics (SCZ) and 23 normal controls (NC) were obtained and volumetric measures were made of an estimate of right and left area 46 (from here on referred to as area 46$_e$). Positive, negative, and disorganized symptoms were rated and IQ scores were obtained. Two working memory tasks sensitive to DLPFC damage (i.e., spatial delayed response and self-ordered pointing) were administered along with a phonemic discrimination control task. The SCZ group performed more poorly than NCs on all cognitive measures, but group differences in brain measurements were not significant. Severity of negative symptoms was associated with poorer performance on IQ measures and one of the working memory tests. These findings suggest that negative symptoms in schizophrenia are associated with general cognitive impairment. Alternatively, reduced IQ in SCZ may be a byproduct of impaired working memory processes and associated executive control deficits. Although brain measures alone were not predictive of negative symptoms, area 46, measures together with IQ accounted for 56% of the variance of negative symptoms. That area 46, measures contributed significantly to the predictive value of IQ suggests that this region may be involved in negative symptoms, but the nature of this relationship will need to be investigated further.

INTRODUCTION

The aim of the present study was to investigate the cognitive and brain abnormalities underlying the negative symptoms of schizophrenia. This is important for several reasons. First, such knowledge may guide us in identifying the neuropathological substrate(s) of schizophrenia. Second, patterns of brain abnormalities may help to clarify diagnostic subtypes within this complex and heterogeneous patient population. Third, valid diagnostic groupings as well as an understanding of the neuropathology of schizophrenia will guide future treatment of this disabling disorder. Finally, identification of brain-behavior relationships in schizophrenia will contribute more generally to knowledge of neurobehavioral contributions to neuropsychiatric disorders.

The notion that schizophrenia is a "brain disease" dates back to 1852 when Belgian psychiatrist Benedict Augustine Morel described a condition in which a young person experienced severe emotional and intellectual disturbance, which he labeled "démence précoce" (cited in Swartz & Africa, 1988). A German psychiatrist, Emil Kraepelin, used the term "dementia praecox" to describe a class of mental disorders that involved both emotional and cognitive impairment that began in adolescence and progressively worsened. It was not until 1913 that Eugen Bleuler, a Swiss psychiatrist, introduced the term "schizophrenia," which means "splitting of the mind," to describe this same phenomenon. Like Kraepelin and Morel, he believed that schizophrenia was a brain disease.

Early studies failed to identify gross brain abnormalities or hallmark histopathological markers of schizophrenia. Since the 1950s, however, when it was discovered that phenothiazines produced substantial improvements in psychotic symptoms, the idea that schizophrenia is due to a neuropathological process became more widely accepted. Numerous investigations of the neuropathological mechanism(s) of schizophrenia followed.

Studies of neuroanatomy using postmortem histology, computed tomography (CT) scans, and magnetic resonance imaging (MRI) have produced contradictory results. While some investigators have found prefrontal cytoarchitectonic abnormalities and decreased volumes of the frontal lobes of schizophrenics on MRI (Andreasen et al., 1986; Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991), others have failed to support these findings (Kelsoe, Cadet, Pickar, & Weinberger, 1988; Suddath et al., 1989). The corpus callosum has been found to be both larger and smaller in schizophrenics compared to normal controls (Bogerts, 1993). Perhaps the most consistent findings have been enlarged ventricles, left hemisphere pathology, reduced volumes of the temporal lobe and limbic structures, and cytoarchitectonic abnormalities within the hippocampus, entorhinal cortex, and parahippocampal gyrus (Bogerts, Meertz, & Schönfeldt-Bausch, 1985; Early, Reiman, Raichle, & Spitznagel, 1987; Golden et al., 1981; Zipursky et al., 1994). Neuropsychological and functional imaging data also have been conflicting, but most consistently point to the involvement of the dorsolateral prefrontal cortex (DLPFC), left hemisphere basal ganglia, and temporo-limbic system (Barta, Pearlson, Powers Richards, & Tune 1990 Early et al. 1987 Saykin et al , 1991, Weinberger Berman, & Zec 1986)

The diverse symptoms of schizophrenia make it unlikely that only one brain region is involved in the pathophysiology of this disorder Individual symptoms may result from disturbances of different brain areas For example, patients who experience hallucinations have been found to have smaller left superior temporal gyri (Barta et al , 1990) than those that do not. In contrast, those with impoverished speech demonstrate decreased metabolism in the DLPFC (Dolan et al., 1993). The majority of studies exploring neuropathological correlates of schizophrenia, thus far, have used single groups of schizophrenics with diverse symptoms. The heterogeneity in symptomatology most likely contributes to the inconsistent findings reported in the literature. By examining relationships between symptoms and regional brain pathology, as in the above studies we may be better able to identify the various brain systems that are involved in producing specific features of the disorder

Other methodological problems encountered in neuroanatomy research are inconsistent definitions of brain areas and measurement techniques. The majority of studies that measure prefrontal cortex or "dorsolateral prefrontal cortex," use arbitrary posterior boundary definitions, such as the anterior-most aspect of the genu of the corpus callosum (Buchanan et al. 1993, Andreasen et al 1986 Kelsoe et al , 1988) This definition of frontal cortex includes orbitofrontal, dorsolateral, ventral medial and anterior cingulate cortices If subtle abnormalities are present in only one or two of these areas, lumping them together would make these differences less likely to be detected. Other studies measure the prefrontal area on only a single slice (Andreasen et al., 1986) which also decreases sensitivity to subtle volume differences. Thus, inconsistent findings reported in the literature may be, in part, the result of techniques that are not sensitive enough to detect abnormalities in specific prefrontal regions. Using neuroanatomic boundaries that are functionally meaningful may increase the sensitivity of MRI measures to volume differences. Indeed, investigators have found this to be true with other brain regions (Foundas, Leonard, & Heilman, 1995, Leonard et al., 1993).

The present study addresses these problems by focusing on a specific region of the brain that is thought to be involved in producing some of the negative symptoms of schizophrenia (e.g., poverty of speech and movement, social withdrawal, flat affect), namely, the DLPFC. Frith (1992) developed a model to describe the information processing deficits and brain regions involved in producing many of the positive (e.g. hallucinations, delusions) and negative symptoms of schizophrenia. He stated that negative symptoms of schizophrenia result from a disorder of "willed action," which he described as behavior that is guided by internal motivations and cues as opposed to being triggered by an environmental stimulus. In order for a an individual to be able to adequately respond to appropriate internal and external cues, he or she must be able to hold information from these environments in mind, attend to appropriate elements of the information, organize that information, and maintain it in short term memory until a response is made. Baddley (1990) defines this constellation of processes as *working memory*. He postulated that short term memory (i.e., working memory) is the role of two slave systems (i e , the phonological loop and visual spatial sketch-pad) that are controlled by an executive system or central processor which allocates attentional resources and is capacity limited Goldman Rakic has drawn on Baddley's theory and has applied it to studying working memory in animals. She describes working memory as an organism's ability to maintain a representation in mind and update it until a response is made (Goldman-Rakic, p. 112, 1992) Her definition differs slightly from Baddley's in that she does not break working memory down into the component processes described above While definitions of working memory may differ to some extent, most theorists agree that working memory is an *active* process of maintaining information in short term memory It is not simply holding information in mind over a delay, rather it involves actively working with that information to transform it or update it over time. Because initiation of social interactions, spontaneous affect and speech are behaviors that are for the most part, internally driven and actively updated, an impairment in willed action/working memory would disrupt these social functions leading to the negative symptoms of schizophrenia.

Frith suggests that the neural system responsible for willed action is a cortico-striato-pallido-thalamo-cortical loop linking premotor areas to subcortical structures According to his model, damage to the dorsolateral prefrontal cortex (DLPFC) or its connections with subcortical structures leads to impaired willed action and the negative symptoms of schizophrenia. Support for this comes from lesion studies which indicate that damage to the prefrontal cortex leads to blunt affect and deficits in initiation and planning (Shallice, 1988, Suss and Benson, 1986) as well as studies linking working memory functions to a subregion within the DLPFC, Walker's area 46 (Goldman-Rakic, 1992; Verin et al., 1993; Walker, 1940). Notably, damage to medial frontal cortex also has been associated with impairments of internally driven behaviors (Passingham, 1993).

The present study drew upon Frith's information processing model with the aim of identifying a brain region(s) involved in producing some of the negative symptoms and cognitive deficits in schizophrenia. Toward this goal, neuropsychological tests that specifically call upon internal initiation of strategies and goals or working memory were administered to schizophrenic subjects. These tests included a test of spatial working memory and a test of nonspatial working memory for a self-ordered sequence of responses. These tasks have been shown to be sensitive to DLPFC damage in humans (Petrides & Milner, 1982; Verin et al., 1993) and specifically with area 46 damage in monkeys (Goldman-Rakic, 1987; Petrides, 1991b).

In the present study, both neuropsychological measures and nuclear magnetic resonance images (MRIs) were obtained and the relationships between area 46, volumes, cognitive performance, and symptom scores were examined. It was expected that more severe negative symptoms, measured by the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), would be associated with poor performance on working memory measures and smaller area 46 volumes. In contrast, it was predicted that negative symptoms would not be associated with the size of other brain regions or non-working memory cognitive performance. Additionally, we expected that working memory performance and area 46 volumes would not be correlated with positive or disorganized symptoms.

Our hypotheses regarding the relationship between working memory and negative symptoms were only weakly supported by the present data; poor performance on the verbal working memory measure was associated with more severe negative symptoms. Intellectual functioning appeared to play a critical role; schizophrenics, as a group, performed more poorly than controls on verbal and performance IQ indices. Additionally, schizophrenics performed more poorly than controls on all of the cognitive measures with the exception of spatial localization. Intellectual performance was highly associated with performance on other cognitive tasks within the schizophrenic group and could not easily be disentangled from working memory performance. Hypotheses regarding the relationship of area 46, volumes to negative symptoms and working memory were only weakly supported. These findings are presented in detail in the Results section and implications are reviewed in the Discussion section.

The following section reviews the literature in areas of schizophrenia, cognitive neuroscience, and neuropsychological research and outlines the hypotheses of the present study. Following the literature review, the Methods section describes the patient and control populations and the neuropsychological and imaging protocols. Findings are presented and reviewed in the Results and Discussion sections, and methodological issues related to our findings are explored in Methodological Considerations. Finally, a summary of our conclusions and directions for future research can be found in the section titled Summary and Future Directions.

REVIEW OF LITERATURE

Definition, Characteristics, and Classification of Schizophrenia

Schizophrenia is a disabling mental illness that can occur suddenly or come on gradually, disrupting an individual's social, occupational, personal, cognitive, and emotional functioning. Characteristic symptoms include distortions of inferential thinking (delusions) and perceptions (hallucinations), disordered cognition, and various deficits in relating to one's environment. Individuals suffering from schizophrenia often describe being invaded by disturbing thoughts, and uncontrolled feelings of fear, anger, anxiety, and sadness. Bleuler (1913/1950) appropriately coined the term "schizophrenia" meaning "splitting of the mind," as in splitting emotions from thoughts and splitting fantasy from reality.

Currently, the DSM classification schemes are among the most widely used for diagnosing schizophrenia in the United States (American Psychiatric Association, 1987, 1994). Descriptions of the DSM-IV characteristic symptoms are provided in Appendix A, Table A.1. DSM-IV symptoms that are associated with schizophrenia, but not central to its definition, are listed in Appendix A, Table A.2.

At this time, most available diagnostic criteria are based on symptom presentation and have little to do with pathophysiology or etiology of the disorder. Five subtypes of schizophrenia are described in the DSM-IV: catatonic, disorganized, paranoid, undifferentiated, and residual. Each subtype is identified by the primary disturbance displayed (see Appendix A, Table A.3). With the criteria provided, clinicians are able to agree whether or not a individual suffers from schizophrenia and label the subtype. Subtypes have been differentiated on the bases of familial patterns, age of onset, and disease course (McGlashan & Fenton, 1991); however, they have not been found to be related to particular neurological, biochemical, and neuropsychological findings.

The subtypes themselves are quite heterogenous. It is rare to find an individual that meets the criteria for one of the DSM-IV subtypes that also does not display symptoms from at least one other subtype. For example, there may be two different individuals that experience both delusions and disorganized thoughts. One of these individuals may be diagnosed as "disorganized" because loose associations predominate, while the other may be diagnosed as "paranoid" because his or her paranoid delusions predominate. A third individual who denies hallucinations, but is paranoid, withdrawn, and lacks initiative also may be diagnosed as "paranoid." These examples illustrate the varied symptomatology that schizophrenics may present with and that, even within subtypes, the heterogeneity of symptoms may be extreme.

The majority of schizophrenia studies place all individuals who meet the diagnostic criteria for schizophrenia into a single group and treat them as a homogeneous sample (Bogerts 1993; Brown et al., 1986; Rubin et al., 1993). The results of such studies have implicated many brain areas as being involved in schizophrenia. Some studies have emphasized the role of the frontal cortex (Stolar, Berenbaum, Banich, & Barch, 1994 Weinberger 1988), while others report involvement of the limbic system (Saykin et al. 1991) and still others have found no significant regional differences between schizophrenic brains and those of normal controls (Kelsoe et al., 1988) However, no single region or pathological mechanism has been identified as being the sole source of the disturbance

The inconsistencies in identifying the neuropathological substrate of schizophrenia are probably in large part, due to the heterogeneity of the disease What is found by one group of researchers may not be confirmed by another group of researchers because their patient populations may be different. For example, in some studies, participants were newly admitted to psychiatric wards (Kelsoe et al., 1988) while in other studies the patients were chronically institutionalized (Johnstone et al., 1978) Newly admitted patients often demonstrate very different and often more severe symptoms than chronically institutionalized patients (Häfner, Fatkenheur, Nowotny & Van der Heiden 1995) Many authors do not provide descriptions of patient characteristics which makes cross study comparisons difficult.

A high degree of variability within a schizophrenic population also may mask potentially relevant differences. For example Andreasen and her colleagues found that schizophrenics cerebral volumes were not significantly different from normal controls (Andreasen et al., 1986) However, when they looked at individual symptoms they found that cerebral size was significantly related to severity of negative symptoms (i.e., alogia, affective flattening, avolition, anhedonia, and attentional deficit).

Because of the symptom overlap between DSM subtypes and the high degree of heterogeneity of schizophrenic symptoms, some researchers have moved to a feature oriented approach to studying schizophrenia neuropathology (Frith, 1992, Stolar et al., 1994). Rather than categorizing people into subtypes, the focus is on individual symptoms or symptom clusters, which are symptoms that have been found to occur together and are statistically related to each other. One of the most well known symptom classifications of this type is that of *Positive* and *Negative* symptom clusters (Crow, 1980).

According to Crow (1980), the positive symptoms of schizophrenia are those that are characterized by a presence of abnormal behaviors or experiences. These symptoms include hallucinations, delusions, and incoherence of speech. Negative symptoms are those that involve a lack of normal behavior or experience such as flat affect, anhedonia and impoverished speech.

In Crow's scheme, positive and negative symptom clusters are statistically unrelated, indicating that one individual may demonstrate both positive and negative symptoms (Crow, 1980). Since they are not mutually exclusive, a high level of symptoms in one cluster does not necessarily predict low levels in the other. Evidence from biological studies support this scheme. Positive symptoms have been found to respond to traditional neuroleptics (i.e., dopamine antagonists), while negative symptoms are more resistant (Angrist, Rotrosen, & Gershon, 1980, Breier et al., 1994, Crow, 1980, Johnstone et al., 1978). The response of positive symptoms to medication has been thought to reflect dopamine overactivity as an underlying mechanism. Negative symptoms, on the other hand, are associated with chronicity, lack of response to traditional neuroleptics and greater cognitive impairment (Andreasen & Olsen, 1982, Angrist et al., 1980, Crow 1980; Johnstone et al., 1978, Strauss, Carpenter, & Bartko, 1974). It also has been suggested that abnormalities of the dopaminergic system underlie both positive and negative symptoms, but that breakdowns in different parts of the system are differentially responsible for the two symptom clusters (Weinberger, 1993, Remington, 1995). Although Crow's theory has been criticized, it remains an important contribution because it was one of the first theories that suggested, and provided evidence for, different underlying biological mechanisms for different symptom clusters.

Since Crow's (1980) positive and negative symptom hypothesis, other symptom clusters have been identified (Bilder, Sukdeb, Mukherjee, Reider, & Pandurangi, 1985, Liddle, 1987, Minas, Klimidis, Stuart, Copolov, & Singh, 1994). Most recently, researcher have begun to regard *disorganization* (inappropriate affect, thought disorder, poverty of content of speech) as a third factor in addition to negative and positive factors (Liddle, 1987).

Because identification of homogeneous subgroups of schizophrenia is difficult, it makes sense to examine the relationship of individual symptoms to brain pathology. There is indirect evidence that some individual symptoms are related to regional brain abnormalities. For example, stimulation of the temporal lobe may result in auditory hallucinations and some patients with temporal lobe epilepsy experience auditory hallucinations (Weinberger, 1993). In addition, patients with prefrontal damage demonstrate symptoms similar to the negative symptoms of schizophrenia (Stuss & Benson, 1986). There also is direct evidence that negative symptoms displayed by schizophrenics are related to prefrontal pathology (Dolan et al., 1993, Stolar et al., 1994), although, contradictory findings have been reported (Wolkin et al.,1992, Young et al., 1991). The aim of the present study was to explore the relationship of negative symptoms to prefrontal pathology further by using both magnetic resonance imaging and neuropsychological measures.

Unlike the DSM-IV subtypes, individual symptoms are relatively independent and can be quantified. These characteristics, along with evidence that negative symptoms may be related to prefrontal pathology provide a good starting point to begin to explore the relationship between symptoms and regional brain abnormalities. Moreover, this approach should not only help to identify the neural mechanisms underlying certain schizophrenic symptoms, but also provide information about the role of the prefrontal cortex in normal behavior and cognition.

Prefrontal Cortex

Behavioral Changes after Prefrontal Lesions.

A remarkable spectrum of behavioral changes has been observed in patients with prefrontal lesions. Some people with prefrontal damage become uninhibited, facetious, and inappropriate (see Damasio & Anderson, 1993, Fuster, 1989, and Stuss and Benson, 1986, for reviews). Others show impaired foresight, poor judgment, and impulsivity

(Eslinger 1985). Still others lose spontaneity, initiative, drive, curiosity, and become abulic and apathetic (Luria, 1962, Stuss 1992). Both depression and euphoria may occur with prefrontal damage and affective expression may be blunted, labile, or inappropriate (Kolb 1980, Parikh, Lipsey, Robinson, & Price, 1988, Stuss 1992). Despite the impressive array of behavioral changes that occur with prefrontal damage, IQ scores have typically been described as within normal limits (Eslinger & Damasio, 1985, Damasio & Anderson, 1993). Damasio and Anderson (1993) describe five hallmark cases of patients with prefrontal damage. What stands out in these cases is normal IQ, with severely altered personality including problems formulating meaningful goals and plans and following through with activities. Most of these patients were unable to hold jobs because of these problems.

Blumer and Benson (1975) described two syndromes of behavioral change in patients with mass lesions and brain trauma affecting the frontal lobes. The first syndrome, *pseudodepression*, occurs with lesions to the anterior lateral and/or medial frontal areas of one or both hemispheres. It is characterized by retardation of all activity and includes features such as apathy, unconcern, lack of drive, poverty of speech, and lack of emotional reactivity (Stuss & Benson, 1986, Stuss 1992, Damasio & Anderson, 1993). The second syndrome, called *pseudopsychopathic*, occurs primarily in individuals with orbitofrontal pathology. The major features of this syndrome are disinhibition, facetiousness, overly sexualized and inappropriate behavior, and lack of concern for others (Stuss & Benson, 1986, Stuss 1992, Damasio & Anderson, 1993).

The first syndrome overlaps conceptually with the negative symptoms of schizophrenia that were described earlier. The focus of the present thesis is to examine the relationship between the negative symptoms and prefrontal pathology in schizophrenia.

The similarities that are seen between patients with prefrontal lesions and those with negative symptoms of schizophrenia have led to the hypothesis that the negative symptoms of schizophrenia are a result of prefrontal pathology or damage to circuitry that involves the prefrontal region. The anatomy of the prefrontal cortex, including its afferent and efferent projections, places it in central position to regulate many behaviors. In order to make sense of the relationship between the negative symptoms and prefrontal pathology, it is important to have an understanding of this circuitry. The following section reviews prefrontal anatomy and its connections.

Prefrontal Anatomy and Connections

The prefrontal cortex makes up approximately 30% of the human cortex (Fuster, 1989). It increases in size with phylogenic development and is presumed to be involved in the highest level of cognitive activity including "consciousness," decision making, abstract thinking, and development of goals and planning (Stuss & Benson 1986, Pandya & Barnes, 1987). However, the precise nature of the functions within the prefrontal cortex remains, for the most part, elusive. Most of our understanding of the prefrontal region comes from experimental lesion studies with rats and nonhuman primates as well as clinical studies of patients with frontal lobe lesions. The assumption of such studies is that if a lesion to a specific brain region produces a specific behavioral deficit, that brain region is responsible for producing that behavior. The limitation of this approach is that the frontal lobes are highly interconnected with numerous other brain regions and lesions of the frontal lobes most likely disrupt functional systems which involve other brain regions. Conversely, damage to an area that projects to the prefrontal cortex will secondarily disrupt prefrontal functioning. The following is a review of prefrontal anatomy, primarily focusing on the connections of dorsolateral prefrontal cortex with other brain regions.

The principal criteria for defining the prefrontal cortex are based on cytoarchitecture, topography, functional characteristics, and fiber connections (i.e. hodology). Topographically, prefrontal cortex lies anterior to the motor and premotor areas in human and nonhuman primates (i.e. anterior to the precentral sulcus in humans and the arcuate sulcus in nonhuman primates, Goldman Rakic, 1987). It is roughly comprised of three surfaces: the dorsolateral convexity, the orbitofrontal surface, and the mesial surface. The dorsolateral convexity is just anterior to the arcuate sulcus in nonhuman primates and surrounds and extends into the fundus of the principal sulcus (Brodmann's area 9, Walker's area 46, Walker, 1940). The orbitofrontal cortex is the ventral portion of the frontal lobes which rests above the orbits of the eyes. This surface is concave on its ventral-most aspect. The orbitofrontal lobe is comprised of Walker's areas 10-14. The medial surface is flat and the surface of each lobe faces each other medially. The medial surface is comprised primarily of Walker's areas 6, 10, 24 and 25, but areas 8 and 9 also extend from the lateral region onto the medial surface.

Walker's (1940) definition of prefrontal regions is based on cytoarchitecture. He differentiated the prefrontal cortex from premotor and motor cortices just posterior to it by the granularization of layer IV and the paucity of large pyramidal cells in layer V. The region around the principal sulcus, area 46, is particularly representative of granular cortex (Walker, 1940). This area has no direct input to motor nuclei and thus only influences motor output in an indirect way (Goldman-Rakic, 1987).

Differential connectivity with other brain regions also indicates functionally distinct prefrontal areas. One of the most widely accepted definitions of the prefrontal cortex is based on projections of the mediodorsal (MD) nucleus of the thalamus to divisions of the prefrontal cortex. The thalamus, particularly the MD nucleus, has extensive bi-directional connections with the prefrontal cortex (Pribram, Chow, & Semmes, 1953; Leonard, 1969, 1972; Jacobson, Butters, & Tovsky, 1978; Alexander et al., 1986). In primates, there are three major divisions of MD defined by cytoarchitecture (for reviews see Fuster, 1989; Leonard, 1972; Pandya & Barnes, 1987). The medial component, called "magnocellular" for the large size of the cells in this region, projects to orbital and medial prefrontal cortex. The lateral component is called "parvocellular" for its relatively small cells and projects to the dorsolateral surface of the prefrontal cortex (i.e. principal sulcus). The extreme lateral aspect of the nucleus, pars paralamellaris, projects to area 8, the frontal eye fields. The region of prefrontal cortex that is relevant for the present thesis is the DLPFC, area 46. Functional differences between area 46 and other prefrontal regions supports the thalamic projections definition of the prefrontal cortex in that area 46 has been specifically linked to spatial working memory abilities while other prefrontal areas have not (Goldman Rakic, 1987 1992, Funahashi Bruce, & Goldman-Rakic, 1989 Fuster 1989, Goldman Rosvold, Vest, & Galkin, 1971, Mishkin & Manning, 1978)

Retrograde tracing methods also have revealed significant projections from other thalamic nuclei including the anterior nuclei the ventral anterior nuclei, the intralaminar nuclei and the medial pulvinar to the dorsolateral prefrontal cortex (Jacobson et al 1978) These nuclei receive diverse subcortical and cortical input from sensory, motor and limbic systems and are in the position of being able to modulate input into the prefrontal cortex (Nauta, 1971 Goldman-Rakic 1987) Goldman Rakic (1987) has proposed that the prefrontal cortex is important for producing behavior guided by information maintained and updated in short term memory, i e., the process of working memory She suggested that the prefrontal cortex mediates such behavior and that the thalamic nuclei may participate as part of a corollary mechanism that monitors and readjusts ongoing behavior (Goldman Rakic 1987) In fact, damage to the MD nucleus of the thalamus in monkeys produced impairment on spatial delayed response tasks similar to that observed following DLPFC damage suggesting an important role for thalamo-cortical and/or cortico-thalamic connections in spatial working memory (Isserhoff, Rosvold Galkin, & Goldman-Rakic, 1982) The role of the prefrontal cortex in working memory will be discussed further below

The DLPFC also has extensive direct bilateral connections with multiple sensory association cortices (Bignall & Imbert, 1968 Pandya & Barnes, 1987 Cavada & Goldman-Rakic, 1989). The connections with posterior parietal cortex are particularly relevant in terms of visuo-spatial functions because this region of cortex receives projections from primary visual cortex and visual association cortex as well as input from multimodal sensory association cortex of the superior temporal gyrus and inferior parietal lobule (Chavis & Pandya, 1976; Pandya and Kuypers, 1969; Petrides & Pandya, 1984). The fact that multimodal sensory information converges in the prefrontal cortex suggest that this information has already undergone associative processing and the DLPFC may be considered "the common end-point for diverse sensory afferent channels [which] is 'privy' to all incoming information" (Goldman-Rakic, 1988, p. 138). A recent functional mapping study using the 14C]2-deoxyglucose method with rhesus monkeys demonstrated increased glucose metabolism specific to the DLPFC and posterior parietal regions during working memory tasks suggesting that these regions may be part of the same functional network (Friedman & Goldman-Rakic, 1994).

Cavada and Goldman-Rakic described three regions (i.e., 7a, 7b, 7ip) within the posterior parietal lobule and a region on the mesial surface of the parietal lobe (7m) that have bi-directional connections with specific prefrontal regions surrounding the principal sulcus (Cavada & Goldman-Rakic, 1989; Goldman-Rakic, 1987). Although the functional significance of these subdivisions is unclear, the fact that they exist suggests that even within the DLPFC there may be functional differentiation. Indeed the greatest deficits on spatial delayed response tasks are seen after damage specifically to the caudal principal sulcus, as opposed to its anterior extent (Goldman-Rakic, 1987). Cavada and Goldman-Rakic (1989) proposed that regions within the principal sulcus may be differentially connected with parietal subdivisions and that there may be subsystems within this larger network that are responsible for a number of sub-functions required for delayed response performance.

The significance of prefrontal/parietal connections is further exemplified by double labeling histology techniques that have shown that the principal sulcus and the posterior parietal cortex are mutually connected to as many as fifteen other cortical areas. This finding also suggests that they both are part of the same functional network (Selemon & Goldman-Rakic, 1988).

In addition to being in a convenient position for integrating multimodal sensory information, the DLPFC, particularly the mid-principalis region, is connected with limbic structures (Pandya & Barnes, 1987; Damasio & Anderson, 1993). Retrograde tracing methods have identified cells in the mammillary bodies and the anterior and posterior cingulate gyrus that project to area 46 (Jacobson et al., 1978). Autoradiographic techniques using amino acid injections into the principal sulcus region reveal significant labeling in the cingulum bundle and retrosplenial areas (Goldman & Nauta, 1977). Furthermore, HRP histochemistry techniques have demonstrated prefrontal connections with the parahippocampal gyrus and the presubiculum as well as extensive connections with the hypothalamus (Jacobson et al., 1978; Selemon & Goldman-Rakic, 1988). The amygdala receives indirect input from area 46 through its connections with the inferior temporal cortex (Nauta, 1971; Porrino, Crane, & Goldman-Rakic, 1981). The hippocampus also receive either direct or indirect projections from the inferior dorsolateral aspects of the prefrontal cortex (Selemon & Goldman-Rakic, 1988; Damasio & Anderson, 1993). Nauta (1971) interpreted these pathways to mean that the cortical representation of the limbic system takes place primarily in the prefrontal cortex. These connections are thought to be involved in monitoring internal emotional and drive states, cortical representation of limbic information, and integration of intellect and feeling (Pandya & Barnes, 1987; Weinberger, 1993).

The basal ganglia receive direct unidirectional projections from the frontal lobes (Alexander et al., 1986; Cummings, 1993a). Alexander et al. (1986) described the presence of at least five loops linking the frontal lobes with the basal ganglia: the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate loops. Each loop circuit receives input from several functionally related cortical areas that send partially overlapping projections to a restricted portion of the striatum. The striatum then projects to the pallidum and substantia nigra where the input is still further integrated. The substantia nigra and pallidum project to a discrete region of the thalamus, which then projects back to a more focused region. Each circuit is partially closed by its thalamocortical projection which terminates in one or more of the multiple cortical input regions.

The dorsolateral prefrontal loop is the loop that is of particular interest here. This circuit begins with cortical input to the dorsolateral portion of the caudate nucleus (Goldman & Nauta, 1977). Projections are heaviest to the head of the nucleus, but significant labeling has been found throughout its length (Goldman & Nauta, 1977). The caudate projects to the lateral aspect of the medial globus pallidus interna and the rostrolateral substantia nigra pars reticulata. Output from these two structure terminates in the parvocellular portions of the ventral anterior and mediodorsal nuclei of the thalamus, respectively. The circuit ends with thalamic projections back to the DLPFC. The five loops remain segregated as they course through these subcortical structures. Mega and Cummings (1994) suggest that the DLPFC circuit mediates "executive" functions, the ability to organize a behavioral response to solve a complex problem. It is hypothesized that this loop may be important with regard to negative symptoms. It also is possible that this loop could be involved in disorganized symptoms since it is thought to be important for planning and organizing behaviors.

Notably, in functional imaging studies, some medial frontal regions, particularly those anterior to supplementary motor cortex, have been identified as being involved in internal generation of responses (Picard & Strick, 1996). Similarly, animals with lesions to medial prefrontal cortex and anterior cingulate regions show deficits in internal response generation (Passingham, 1993). Medial and dorsolateral frontal cortices are bidirectionally connected and it is likely that they are different parts of a common circuitry important for response selection and internal generation of behavior.

The DLPFC cortex has indirect connections with primary motor cortex through its connections with supplementary motor and premotor cortices, as well as the frontal eye fields and cingulate cortex (Arikuni, Sakai, Hamada, & Kubota, 1980; Selemon & Goldman-Rakic, 1988; Lu, Preston, & Strick, 1994). The superior colliculus also receives projections from DLPFC (Goldman & Nauta, 1976). Furthermore, the DLPFC is intimately connected to other prefrontal regions such as the orbitofrontal and mesial frontal cortices, which are primarily related to limbic and motor functions, respectively (Selemon & Goldman-Rakic, 1988; Cummings, 1993a). Middleton and Strick (1994) used herpes simplex virus type one retrograde transport methods to demonstrate that areas of the brain that are known to be involved in motor functions, the globus pallidus and the cerebellum, project to area 46. These findings suggest that the DLPFC receives feedback from motor systems, which probably serves the purpose of modulating motor responding.

To summarize, the DLPFC receives information about the outside world through its connections with sensory and multimodal association cortices as well as through thalamic relay nuclei. It also receives information about the organism's internal state through its connections with limbic structures and the hypothalamus. The reciprocal connections with these areas suggests that the DLPFC is in a position to send feedback to these brain areas, possibly influencing its own afferents. Furthermore, since the DLPFC is not directly connected to primary motor neurons, but instead sends projections to premotor cortex, SMA, the basal ganglia, and the superior colliculus, it is in a strategic position to guide motor responding in the planning and initiating stages.

Dorsolateral Prefrontal Cortex and Spatial Working Memory in Animals

The DLPFC has been shown to be involved in the process of working memory (Funahashi et al., 1989; Fuster, 1989; Goldman-Rakic, 1987, 1992; Verin et al., 1993), which Goldman-Rakic (1987) defines as an internal representation that is actively maintained and updated in short term memory. Through numerous studies with nonhuman primates it has been demonstrated that the DLPFC is particularly important for *spatial* working memory. Spatial working memory has been assessed in monkeys by means of a task paradigm known as *delayed response*. In the prototypical delayed response (DR) task, an animal sees the experimenter hide a food reward in one of two food wells. The food wells are covered with opaque mats and a screen is then lowered in front of the food wells. After a specified delay, the screen is raised and the animal is required to respond to the location where the food was hidden. If the response is correct, the animal receives the reward. This is a working memory task because the animal is required to hold the spatial information in mind during the delay and at the time of the response, there is no external cue to indicate the correct location. This is in contrast to a conditional memory task during which a stimulus from the environment signals the correct response. For example, in a conditional response task, a reward may always be hidden in a food well covered by a red mat. The subject is required to call from long term memory the associational rule that "red = reward." Because the response is dictated by a stimulus in the environment, working memory is not required once the task has been learned.

Monkeys with bilateral lesions of the DLPFC (Walker's area 46) perform poorly on delayed response tasks, while performance on conditional memory tasks remains intact (Goldman et al., 1971; Goldman Rakic, 1987). In a lesion study using naive rhesus monkeys, Goldman et al. (1971) demonstrated that some regions within the DLPFC are more important for spatial working memory than others. They used two different versions of the DR task. One version was the same as that described above. The second was a delayed alternation (DA) task. On the first trial of a DA task, food rewards are hidden within two food wells. The monkey does not see the experimenter bait the wells but is signaled to choose one of the wells. Since both wells are baited, they automatically receive a reward on the first trial. On the second trial, a reward is hidden only in the food well that was not previously chosen. The remaining trials continue with this alternating pattern. Like DR, this task requires an on-line representation of a previous occurrence (i.e. spatial working memory) for successful performance. These authors found that monkeys with lesions confined to the principal sulcus (PS) region were impaired on both DR and DA, while those with arcuate sulcus (AS) lesions and superior dorsolateral lesions were not. In addition, lesions in brain regions with known connections to the principal sulcus region (e.g., caudate nucleus) result in deficits similar to those resulting from DLPFC lesions (Goldman & Rosvold, 1972).

The role of the DLPFC in working memory has been further clarified by single cell recording studies (Funahashi et al., 1989; Fuster, 1989). Funahashi et al. (1989) demonstrated that during an oculomotor DR task, a large subset of neurons within the monkey PS region become active. Many of these neurons become active the moment the stimulus disappears from view and remain active until the animal delivers a response. This finding suggests that these cells are likely to be involved in keeping information "on line" during the delay. Of the neurons with delay activity, 79% were directional, i.e. demonstrated different discharge rates according to cue location. Thus, the PS neurons seem to be spatially sensitive. Moreover, some investigators have reported delay enhanced discharge during delayed response tasks in key structures with which the PS is connected, e.g., hippocampus, head of the caudate nucleus, and the mediodorsal nucleus of the thalamus (Fuster & Alexander, 1973; Goldman-Rakic & Friedman, 1991).

Functions of the Prefrontal Cortex in Humans

The prefrontal cortex has been described as the brain's "executive system" because it integrates and modulates cognitive, sensory, and motor functions (Stuss & Benson, 1986; Damasio & Anderson, 1993). The executive system is involved in activities such as establishing goals, planning, following through with tasks, shifting strategies, inhibiting inappropriate responses, and problem solving (Shallice, 1988; Passingham, 1993). Its central relationship with limbic and sensory systems also puts the prefrontal cortex in a strategic position to mediate internal and environmental influences on behavior (Nauta, 1971). Attention and memory functions, which are also necessary for performance of executive functions have also been found to be impaired with prefrontal damage (Stuss & Benson, 1986; Shallice, 1988).

Experimental findings of DLPFC functions

A number of experimental procedures have been developed to test executive functions. Foresight, formulation of goals, and planning competence have been tested with the Tower of Hanoi or the Tower of London Task. Shallice (1982) reported that patients with left anterior lesions (i.e. fronto-temporal and fronto parietal) were impaired while those with right or left posterior lesions did as well as normal subjects.

Deficits on making *cognitive estimations* are also seen with frontal damage (Shallice & Evans, 1978). When asked questions such as, "How fast do race horses gallop?" or "What is the length of an average man's spine?" patients with frontal damage of various etiologies tend to give extreme responses (i.e. too low or too high) compared to normal controls and patients with posterior damage. This ability is not lateralized. "Answering such questions satisfactorily stresses the abilities of selecting an appropriate cognitive plan and of checking any putative answer obtained as much as the ability of carrying out the selected plan" (Shallice & Evans, 1978, p. 295).

Lhermitte (1983, 1986) has used two unique paradigms to demonstrate that frontal patients have an exaggerated dependence on cues from the outside environment. In one paradigm he assessed *utilization behavior*, the tendency for an individual to reach for and use objects in their immediate environment, even when inappropriate (Lhermitte, 1983). The examiner placed random objects on the table and watches for the patients' reactions. Patients with focal lesions of the prefrontal cortex due to vascular infarct, tumor, or trauma pick up the objects (e.g. a comb, eye glasses) and start using them (i.e. combing their hair, put glasses on) significantly more often than controls. In the second paradigm, he assessed *imitation behavior* (Lhermitte, 1986). The experimenter performed random and inappropriate gestures during testing and, without instruction to do so, some patients with prefrontal lesions imitated their gestures. In contrast, control subjects never imitated the gestures of the experimenter. While not all patients with prefrontal damage demonstrated these behaviors, almost all of the patients who did demonstrate these behaviors had frontal lobe injuries (28 out of 29), which were usually large, unilateral (left or right), and inferior (i.e., orbital). These patients seem to have difficulty inhibiting the motor routines that have been activated by these stimuli.

Several atypical memory deficits have been described in patients with prefrontal damage. Anecdotally, there have been reports of patients with normal or superior recall on traditional tests of memory (e.g. Wechsler Memory Scale) who are extremely impaired in their daily lives. These individuals may misplace things, miss appointments, and leave lights and appliances on when they leave a room (Stuss & Benson, 1986; Damasio & Anderson, 1993). This phenomenon has been termed *forgetting to remember* (Damasio & Anderson, 1993).

A related phenomenon, impairment of *metamemory*, involves poor ability to judge one's own memory abilities. This has been demonstrated with the *feeling of knowing* paradigm which requires individuals to estimate how accurate their performance on a recognition memory task will be. Korsakoff patients, who have diencephalic amnesia as well as prefrontal impairment, overestimate their performance compared to normal controls and other amnestics (Shimamura & Squire, cited in Bauer, Tobias, & Valenstein, 1993). Because other amnestics performed normally on this task, it has been hypothesized that the metamemory deficit seen with Korsakoff patients is a function of possible frontal pathology.

Another memory deficit seen in frontal patients is impaired recall of the source of information, or *source amnesia*. In one experiment, participants were taught facts in the laboratory setting. Hours or days later, when answering questions about these facts, they often incorrectly reported having learned the facts from a source outside the laboratory, or, vice versa (Janowsky, Shimamura, & Squire, 1989). Frontal patients made these errors significantly more often than normal controls.

Other deficits that occur with prefrontal damage include impaired recency or frequency judgments, memory for temporal sequence of events, poor use of contextual information in organizing information for storage, and sensitivity to interference from previously presented information, also known as *proactive interference* (see Bauer et al., 1993; Damasio & Anderson, 1993; Lezak, 1995, for reviews).

Given the interaction of the frontal lobes with sensory, limbic, and motor systems, it makes sense that patients with frontal lesions demonstrate problems inhibiting responses, developing strategies, and making abstract judgments. Furthermore, their memory problems are not surprising. As described earlier, research with nonhuman primates strongly implicates the prefrontal region as important for working memory. The above findings indicate that temporal order memory, metamemory, and source memory are all impaired in patients with prefrontal damage. Importantly, these patients are not amnestic in the traditional sense. That is, their associative memory remains intact. Damasio and Anderson (1993) reported neuropsychological data from eight patients that suffered prefrontal damage from vascular incidents or surgical excision of tumors. With few exceptions, these patients performed within normal limits on a verbal list learning task (i.e., Rey Auditory Verbal Learning Task), immediate and delayed recall of paragraphs, and paired associate learning. These findings suggest that patients with frontal lesions are able to access memory for information that they have previously been exposed to; however, when asked to compare an internal representation with one or more pieces of information and make judgments about them, they are impaired. In this sense, their impairment is similar to the working memory deficits described in monkeys with area 46 lesions. In each case, the subject is asked to hold information "on line" while they make some sort of comparison with either another internal representation, or a stimulus from the environment. The problems that patients with prefrontal lesions have on nontraditional memory tests are consistent with their difficulties abstracting and using internal representations to guide behavior on tests that were not originally intended to test memory functions like the Tower of London test (Goldman Rakic 1987)

Neuropsychological findings of DLPFC functions in humans

A number of neuropsychological tasks some of which are similar to the experimental tasks, are used to assess the functional integrity of the prefrontal cortex. The Wisconsin Card Sorting Test (WCST) was originally developed as a measure of abstract reasoning and flexibility of thinking (Grant & Berg, 1948) Deficits on the WCST have been reported following large unilateral excisions of the superior frontal region, usually including DLPFC and large midline prefrontal tumors (Lhermitte, 1986, Milner 1962,1963) While patients with frontel lesions are able to identify the correct sorting categories, they have problems shifting from one sorting principle to another Patients with left DLPFC lesions were more impaired than patients with orbitofrontal or posterior lesions Performance of normal individuals on the WCST has been associated with increased regional cerebral blood flow (rCBF) in the left DLPFC measured in studies using single photon emission computed tomography (SPECT Rezai et al , 1993).

Some researchers have found impairments on the WCST following both frontal and non-frontal lobe (i.e, parietal and occipital) damage due to cerebrovascular accidents or surgical resection (Anderson, Damasio, Jones, & Tranel, 1991). Qualitatively the number of perseverative responses was more associated with prefrontal damage than the other scoring criteria. Lezak (1995) reviewed several other studies that implicated the temporal lobes and diffuse brain pathology in poor performance on the WCST. There does not seem to be much question that WCST is sensitive to frontal damage. However it is not specific. Poor performance does not necessarily localize impairment to the frontal lobes. Convergent evidence from performance on other cognitive tasks is necessary to make judgments about lesion location.

A similar task, Halstead Category Test (HCT) also requires flexibility in thinking and abstract concept formation. The HCT has more dimensions than the WCST and therefore is more difficult. It also requires rule learning, while the WCST involves attribute identification (Lezak, 1995). Although the cognitive requirements of this task would seem to implicate the prefrontal area, based on a number of findings, Stuss and Benson (1986) regard this test as sensitive for brain damage without localizing function.

Problems inhibiting responses are seen when patients with frontal lesions are required to override an established, well learned, or automatic response pattern with one that is novel or less automatic (Perret, 1974; Leimkuhler 1985). Difficulty in inhibiting prepotent responses can be observed in a variety of situations, such as Lhermitte's utilization paradigm discussed earlier. The term "perseveration" is used when the inappropriate response is made repeatedly. This behavioral characteristic can be seen in many situations. For example, an individual may give the same response to several different questions. On the WCST he or she may continue to sort to the wrong principle in the face of negative feedback (Milner, 1964; Anderson et al., 1991). Patients with frontal lesions also are impaired on tests designed specifically to test inhibition ability such as the Stroop Interference Procedure (Stroop 1935) and Luria's (1962) Go-No-Go paradigm (Luria, 1962 Perret, 1974 Leimkuhler 1985)

Perseveration is also common on tasks that require creative thinking or internally generated responses such as Controlled Oral Word Association (COWA Benton & Hamsher, 1989). Impairments on the COWA are regularly seen with unilateral prefrontal excision or lesions, especially involving the left hemisphere (Milner 1962 Benton, 1967 Perret 1974) Successful performance on COWA not only requires the ability to inhibit old or inappropriate responses but also the ability to initiate an organized lexical search, keep pertinent verbal information in mind, and access an intact store of lexical information Reduced capacity to generate words has also been associated with dementia and aphasia in the absence of gross frontal pathology (Stuss & Benson, 1986 Lezak, 1995) In a PET study of normal individuals, performance of both letter and category versions of COWA was associated with increased blood flow to the left DLPFC (Frith, Friston, & Liddle 1991a) Consistent findings with normal subjects have been reported using a verb generation task with FMRI techniques (McCarthy et al., 1993) Generation of random finger movements also has been associated with increased rCBF to the DLPFC bilaterally (Frith et al., 1991b). These findings suggest that the generative component of COWA and other nonverbal generation tasks depend to a great extent on the prefrontal region.

Impaired performance on Design Fluency a task that has been described as a nonverbal analogue of COWA, is seen in patients with unilateral surgical excisions of the superior frontal lobes (Jones-Gotman 1977, Lezak, 1995) While patients with left frontal or temporal lobe lesions were also somewhat impaired, the right frontal patients produced significantly more perseverative, and fewer novel responses.

As discussed earlier, the ability to plan and follow through with plans is often devastated in patients with frontal injuries (Damasio & Anderson, 1993; Shallice, 1982). Like the Tower of London task, the Trail Making Test requires planning and sequencing abilities. Patients with prefrontal tumors are impaired on this test (Leimkuhler, 1985). However, some patients with large bilateral prefrontal lesions are unimpaired, while some patients with damage outside of the frontal lobe are also significantly impaired, suggesting that it is a nonspecific test of brain damage (Lezak, 1995, Stuss & Benson, 1986). However, Stuss and Benson (1986) state that, qualitatively, patients with frontal lesions may be distinguished from other patients in their qualitative performance. They tend to be very disorganized in their approach to the task and fail to maintain set more frequently than patients without frontal lesions.

Similarly, Milner (1962) found that although patients with temporal lobe excisions were impaired on a stylus maze learning task and required significantly more learning trials than those with frontal and posterior excisions, patients with either left or right frontal excisions made qualitatively distinct errors. Despite constant feedback, they broke the rules of the task more often than non-frontal patients and repeated errors almost 10 times as often. These findings support previous reports of frontal damage resulting in an inability to inhibit inappropriate responses, a tendency to perseverate, and difficulty keeping instructions in working memory during the task (Milner, 1963; Shallice, 1988).

Short term retention is also considered to be an important function of the prefrontal lobes. The Brown Peterson Technique, or consonant trigrams, is a common technique used to measure short term retention in the face of distraction (Peterson & Peterson, 1958). Korsakoff patients were highly susceptible to distraction and performed poorly on this task, which these authors attributed to their prefrontal pathology (Butters & Cermak, 1975). Lezak (1995) indicated that patients with left hippocampal resection are also impaired on this task. Again this task seems to be sensitive, but not specific to prefrontal damage.

Other functions that have been attributed to the prefrontal region include selective attention, motor sequencing, verbal abstraction, categorization, and general sequencing abilities (Luria, 1962; Stuss & Benson, 1986; Fuster, 1989; Damasio & Anderson, 1993; Lezak, 1995). This extensive list of functions does not exhaust the various deficits that have been observed with prefrontal injuries. What can be gleaned from this review is that the prefrontal region is involved in wide range of functions including planning, formulating strategies, inhibiting over learned or inappropriate responses, and keeping information in short term memory. Most of the tests described above are sensitive to, but not specific to prefrontal pathology. This is not surprising given the wealth of connections between this region and other cortical and subcortical brain structures. Furthermore, because brain lesions in humans are rarely isolated to specific subregions within the prefrontal cortex, little can be said about the functional specificity of the different subdivisions.

Researchers studying nonhuman primates have been more successful in developing tests that are both sensitive and specific to individual brain regions, even within the prefrontal cortex (Goldman-Rakic, 1987). As described earlier, Goldman-Rakic and others have ascribed the fairly specific role of working memory to the prefrontal cortex (Goldman-Rakic, 1987; Funahashi et al., 1989). Goldman-Rakic (1987) suggests that many of the deficits that human patients with frontal lesions demonstrate can be explained as impaired working memory. For instance, performance on the WCST requires working memory in the sense that there is no stimulus cue in the environment to guide an individual's response. The subject must rely on internal representations of abstract concepts and feedback received on preceding trials in order to perform the task successfully. Similarly, the Tower of London Task requires internal visualization or planning without the aid of an external cue. The COWA task, mazes, and design fluency all have the same common denominator: no cue in the environment indicates the correct response.

If the prefrontal cortex does indeed allow us to hold information "on line" until a response is made, we would expect humans with prefrontal lesions to demonstrate the same kinds of working memory deficits that have been found with monkeys. In fact, some researchers have examined the performance of patients with prefrontal lesions on some of the DR tasks that were originally designed for use with nonhuman primates. These findings are reviewed in the following section.

Delayed response in humans with frontal lesions

While the relationship between DLPFC and DR performance has been well established within the animal literature, attempts to apply the DR paradigm to humans have been somewhat controversial. Application of the delayed response task to humans has been difficult for several reasons. First, the nature of the DR task may be different for humans and monkeys. Many "nonverbal" tasks are often contaminated by the natural human tendency to apply language in most situations. They may use language to guide their responses in a way that is not available to nonhuman primates. Second, difficulty thresholds vary between species, resulting in possible ceiling or floor effects. Third, while most animal studies exploring the function of DLPFC are lesion studies, it is difficult to find human subjects with lesions confined to area 46 within the DLPFC. Finally, even when lesions are relatively focal, the location of the human correlate of the PS region (area 46) is not entirely clear.

Ghent, Mishkin, and Teuber (1962) reported that patients with frontal lobe lesions, as a result of penetrating brain wounds, performed comparably to normal controls on four tests of spatial working memory. These authors did not specify the specific areas of damage within the frontal lobes, nor did they describe the extent of the lesions. While they attempted to avoid the confound of language by using stimuli that could not be easily verbalized, the result was that their tasks bore little resemblance to the working memory tasks used with animals. Using a traditional delayed alternation (DA) task, Chorover and Cole (1966) found that although patients with frontal lesions performed worse than controls, a group of patients with lesions outside of the frontal lobes were impaired as well. They concluded that DA relied on the integrity of the brain as a whole and could not be localized to the frontal lobes. However, the "non-frontal" group was comprised primarily of individuals with tumors. Although the tumors were not themselves in the frontal lobes the tumors were large and it is possible that mass and pressure effects of tumors may have had remote effects on the frontal lobes or related regions, such as the basal ganglia, resulting in "frontal lobe" symptoms.

A series of studies conducted by Oscar-Berman and her colleagues examined the performance of patients with alcoholic Korsakoff syndrome on traditional DR tasks (Oscar-Berman & Zola-Morgan, 1980; Oscar-Berman, Zola-Morgan, Öberg, & Bonner, 1982; Freedman & Oscar-Berman, 1986). Korsakoff's syndrome is thought to primarily affect diencephalic structures resulting in severe anterograde amnesia as well as graded retrograde amnesia (Butters & Cermak, 1980). In addition, Korsakoff patients are known to demonstrate a number of symptoms, such as apathy, confabulation, and blunted affect which are consistent with frontal lobe pathology. Oscar-Berman and Zola-Morgan (1980) found that Korsakoff patients were impaired on both spatial DA as well as visual pattern reversal. A later study from this same laboratory confirmed the DA findings and also revealed that Korsakoff patients were impaired on spatial DR. While it is tempting to conclude that the deficits demonstrated by Korsakoff patients on DR tasks are a result of abnormalities within the dorsolateral prefrontal cortex, not enough is known about the neuropathology of the Korsakoff syndrome to make such a conclusion.

In one study, a group of patients with focal ischemic lesions to the DLPFC were tested on a series of spatial DR tasks (Verin et al., 1993). Patients with frontal lobe lesions were impaired on almost all the tasks relative to normal controls and patients with focal ischemic post-central lesions. Their main difficulty was changing strategies and they showed a tendency to produce previously correct responses (i.e., perseverate). Interestingly, on the initial DA task, patients with frontal lesions performed better than controls, i.e., almost perfectly. It seemed as though they made no attempt to develop a strategy and automatically fell into a routine of alternating their responses. In contrast, the two control groups made several errors as they tried various strategies before settling for one. The authors concluded that one of the functions of the frontal lobe is to "elaborate goal-directed programmes and permit their expression by the inhibition of more automatic activities. This loss of ability to inhibit stereotypes" may account for the performance of frontal lobe patients in this study.

Functional imaging studies also support the central role of DLPFC in spatial working memory. Activation of the DLPFC (i.e. areas 46 and 9) has been found using PET in normal humans during performance spatial working memory task (McCarthy et al., 1994). These authors reported bilateral activation, with the right hemisphere showing more activation than the left. Similarly, Jonides et al. (1993) reported a PET study which revealed activation primarily in the DLPFC in the right hemisphere of normal human subjects during a spatial working memory test. The focus of this activation, however, was in area 47 which is just ventral to area 46 and, therefore, not entirely supportive of central role of DLPFC in spatial working memory in humans. Activation also was found in the right occipital lobe, parietal lobe, and premotor cortices, which are all considered to be part of working memory circuitry (Jonides et al., 1993; Goldman-Rakic, 1987).

Thus, spatial working memory in humans does seem to rely, at least to some extent, on the integrity of the DLPFC. On spatial DR tasks that closely resemble those used in the monkey literature, patients with specific DLPFC abnormalities were impaired in at least one study. However, the extent of involvement of other brain regions for human DR performance is not clear.

Importantly, there appear to be some discrepancies between the way working memory is conceptualized within the animal literature versus the human literature. Within the animal literature, traditional working memory tasks require animals to hold information in mind over a delay and produce a response with no external cues to guide behavior. Within the human literature it is common to impose distraction during the delay and/or require some active manipulation of the information in memory. When longer delays and more complex tasks are used with animals, lesions of mesial temporal structures also impairs performance.

Goldman-Rakic and her colleagues assigned a very specific role to the DLPFC in monkeys, namely spatial working memory (Goldman-Rakic, 1987, 1992). While the data support this, there is also evidence that DLPFC is involved in working memory of a nonspatial nature (Petrides & Milner, 1982; Petrides, 1991a, 1991b; Petrides, Alivisatos, Meyer, & Evans, 1993). Petrides (1991b) found that monkeys with lesions to areas 46 and 9 were impaired on a task that required self monitoring and memory of previous responses (condition A). In contrast, the animals' ability to visually discriminate previously viewed stimuli from novel stimuli remained intact (condition B). In condition A, the animals were presented with 3 objects. They were allowed to displace one of the objects to obtain a food reward. Immediately after this presentation, an opaque screen was lowered to hide the objects. When the screen was raised, the monkey saw two objects. One of the objects was that previously selected by the animal and the other object was one of the two that were not selected. In order to receive the food reward, the monkey was required to displace the object that was not previously chosen. In condition B, the sequence of events was almost identical with the exception that during the test phase, the object that was chosen on the preceding presentation was paired with a novel object. The monkey was required to choose the novel object in order to receive the food reward. As indicated above, monkeys with lesions to areas 46 and 9 were impaired on condition A, but not B, indicating a specific deficit in recalling previous responses. The locations of the objects in these tasks were random, arguing against spatial working memory deficits.

Petrides and Milner (1982) reported a similar deficit in human subjects who had undergone unilateral frontal excisions for relief of pharmacologically intractable epilepsy. These authors used a set of four tasks which they called a "self-ordered pointing" tasks. Each of the four tasks involved a different type of stimuli: abstract designs, representational drawings, high imagery words, low imagery words. Subjects were presented with a serial sequence of pages one at time. The same set of stimuli was presented on each page, but the position of the stimuli changed from page to page. Subjects were required to point to a different stimulus on each page until all the stimuli had been selected. In order to perform this task, one needs to be able to "initiate a sequence of responses and carry them out with constant monitoring of their execution" (Petrides & Milner, 1982, p. 249). In other words, the task requires working memory for self-initiated responses. This tasks differs from spatial delayed response tasks in that in addition to having no cue from the environment to guide behavior, it requires active updating of short term memory with *new* information over a period of time. Patients with frontal lobe excisions were impaired on all four tasks relative to normal controls. Left frontal lobe lesions impaired performance on all four tasks, while right frontal lobe lesions affected performance only on the two nonverbal tasks. The authors hypothesized that the left hemisphere may play a dominant role in the programming of responses and they suggested that an active working memory may be dependent on the left hemisphere for some degree of verbal mediation.

In two PET studies, Petrides and colleagues found activation in the mid-DLPFC (areas 46 & 9) during self-ordered tasks (Petrides et al., 1993; Petrides, Alivisatos, Evans, & Meyer, 1993). For the nonverbal version, activation was bilateral, but greater in the right DLPFC. The verbal working memory tasks produced strong activation in both the right and left DLPFC.

Neuropsychological Findings in Schizophrenia

Methodological Considerations

Neuropsychological studies of schizophrenia have lead to a number of conflicting and complicated findings. Some investigators have interpreted their findings as supporting generalized bilateral dysfunction with no localized dysfunction (Blanchard &

Neale, 1994). Others have reported impairment of the prefrontal region or deficits lateralized to the left hemisphere (Flor-Henry & Yeudall, 1979; Weinberger & Berman, 1988). Still others have found differential impairments of the frontotemporal system or the temporolimbic system (Saykin et al., 1991; Weinberger, Berman, Suddath, & Torrey, 1992).

There are a number of methodological issues in this research that are likely to be the cause of these conflicting findings. First, the medication status of research participants may confound the data. For instance, anticholinergic medication, which is given to treat the extrapyramidal effects of the neuroleptic medication, has been found to impair memory on neuropsychological tests (Fayen, Goldman, Moulthrop, & Luchins, 1988; Gold & Harvey, 1993). Thus, interpretation of cognitive impairments observed in these subjects may be complicated by the side effects of medication. Some investigators have suggested that dopaminergic drugs affect frontal metabolism and possibly cognitive functions as well (Early et al., 1987). There is evidence of increased caudate volume with neuroleptic treatment (Chakos et al., 1994). However, other investigators have reported no effects of neuroleptics on cognitive functions, and some have even reported improved cognitive function with medication (Rupniak & Iversen, 1993).

Second, some important demographic variables are often not always controlled. Education is a particularly complicating factor because schizophrenic individuals typically develop their illness in late adolescence or early adulthood, which may interfere with any plans for higher achievement and educational goals. Because their reduced educational attainment is part of their syndrome, it does not make sense to match them with controls based on education. It has been suggested by some investigators that parental education is a more appropriate variable for balancing patients with controls (Gur, Gur, & Saykin, 1990). In addition, gender has been found to be a significant factor in schizophrenic research, with male subjects demonstrating a more chronic course and greater extent of brain abnormalities than females (Andreasen et al., 1990).

Third, there is no consensually agreed upon approach to sampling neuropsychological functions in studies of schizophrenia. Therefore, comparisons between studies is difficult, if not impossible, since a wide array of different tests is used. While some investigators administer a narrow range of neuropsychological tests designed to test specific brain functions, others use extensive batteries in an effort to determine patterns of cognitive function/dysfunction. This is a significant problem with neuropsychological studies because in order to establish that a particular function is differentially impaired, it is necessary to administer a wide range of tests. This establishes a general background against which specific functions can be compared. For example, if an individual performs two standard deviations below the norm on a verbal memory test, one might assume that he or she has a severe verbal memory impairment. However, if that same individual was two standard deviations below the norm on most language tests, with and without memory components, one might conclude that his or her language impairment interfered with verbal memory performance. Moreover, if this person were two standard deviations below the norm on most cognitive tasks, the problem would be seen as one of diffuse cognitive dysfunction, rather than a specific language or memory deficit. This example illustrates the danger of drawing conclusions based on performance on any individual task. However, administering an entire battery of neuropsychological tests that assess all areas of cognitive functioning would be extremely labor intensive and patients might not be able to withstand the testing.

Fourth, as previously discussed, the heterogeneity of schizophrenia presents a significant confound in the majority of neuropsychological studies with this patient population. Extreme variance within and between patient groups may "wash out" potentially important differences. Exploring the neuropsychological deficits associated with specific signs and symptoms of schizophrenia avoid the problem of heterogeneity of symptoms and has recently become more popular (Frith, 1992, Stolar et al., 1994). We have adopted this strategy and will explore the relationship between specific negative symptoms and structural and functional brain abnormalities of the DLPFC.

Another concern is that neuropsychological studies of prefrontal functions, in particular, suffer from our lack of knowledge about the functions of specific subdivisions of the prefrontal cortex. The term "frontal lobe tests" refers to tests that reveal deficits in patients with tumors, vascular insults, penetrating wounds, closed head injuries, and other diseases that affect frontal cortex. It is rare to find patients with discrete lesions in specific regions of the prefrontal cortex such as the DLPFC (Shallice, 1982, Stuss & Benson, 1986). Furthermore, areas within the prefrontal cortex are highly interconnected and damage to one region may produce deficits similar to damage to neighboring regions (Goldman-Rakic, 1987).

Finally, as mentioned earlier, most of our knowledge about the anatomy and regional functions of the prefrontal cortex has come from animal lesion studies. The human prefrontal cortex is more morphologically different from nonhuman primates than other cortical areas and, most likely, is functionally different as well. The prefrontal cortex is the "executor" of higher cognitive functions, of which language plays a crucial role. Because animals do not have language, very little is known about the role of localized prefrontal areas in language functions or the interaction of language with other executive functions. Thus, generalizing from results of monkey studies to human cognition may be dangerous.

With these issues in mind, it should be recognized that poor performance on "frontal lobe tests" does not confirm the existence of pathology specific to prefrontal regions. Other cognitive deficits found in schizophrenia will be described briefly later, which will help to qualify the nature of the frontal deficits described below.

Neuropsychological Deficits in Schizophrenia

It is generally accepted that schizophrenics perform more poorly than normals on a wide range of cognitive tests. With a group of unmedicated schizophrenics, Saykin and his colleagues found that patients performed at least one standard deviation below the mean of the normal control group matched for age, parental education and occupation level, handedness, and race, on all tests from a large battery of tests administered, including the Wechsler Adult Intelligence Scale-Revised (Saykin et al., 1991). Other investigators have reported similar findings (Goldberg et al., 1990; Kolb & Wishaw, 1983; Stolar et al., 1994). Against this background of general cognitive dysfunction, differential deficits on tests sensitive to frontal lobe damage are evident from a number of studies that have used moderate to extensive test batteries (DeQuardo et al., 1994, Goldberg et al., 1990; Goldberg, Weinberger, Berman, Pliskin, & Podd, 1987, Keilp et al., 1988, Seidman et al., 1994, Sweeney, Haas, & Shuhus, 1992).

Deficient performance on the WCST by patients with schizophrenia is a consistent finding (DeQuardo et al., 1994, Kolb & Wishaw, 1983, Seidman et al., 1994, Sweeney et al., 1992). The types of deficits reported are, primarily, completion of fewer categories than normal controls and increased perseverative errors and perseverative responses. While patients' performance can be normalized with explicit card-by-card instructions, Goldberg et al. (1987) found that when the instructions are withdrawn, they return to their poor baseline performance. The impairments demonstrated by schizophrenics on the WCST have been described as problems with working memory, shifting strategies, abstract concept formation, and problem solving (Damasio & Anderson, 1993, Gold & Harvey, 1993, Goldberg et al., 1990, Lenzenweger & Korfine, 1994, Morice, 1990, Saykin et al., 1991, Sullivan, Shear, Zipursky, Sagar, & Pfefferbaum, 1994, Van der Does & Van den Bosch, 1992).

Deficits on the Trail Making Test are also commonly reported (DeQuardo et al., 1994, Goldberg et al., 1990, Keilp et al., 1988, Malec, 1978, Sweeney et al., 1992). Impairments usually manifest as slow performance on Trails B. Liddle and Morris (1991) reported that 91 percent of their group of 49 schizophrenic patients performed in the impaired range. Poor performance on this task is more likely to occur in chronic schizophrenics with multiple psychotic episodes (Sweeney et al., 1992).

There is substantial evidence that schizophrenics are impaired on COWA (Sweeney et al., 1992; Allen, Liddle, & Frith, 1993; Crawford, Obonsawin, & Bremner, 1993). On a category version of the task, they produced fewer words than normal controls, showed less semantic clustering of words, and produced words that were not in the category requested (Allen et al., 1993). Liddle and Morris (1991) found that 52 percent of their group of patients fell in the impaired range on a word generation task using the letters F, A, and S.

In one study the influence of general verbal deficits on COWA was controlled for with a regression equation that predicted COWA scores based on age and VIQ (Crawford et al., 1993). Schizophrenic patients performed significantly worse than controls and their performance was significantly worse than predicted by the regression equation.

Very few studies have looked at design fluency in schizophrenia. However, Kolb and Wishaw (1983) found that schizophrenics tended to perseverate on the same or similar designs, while controls were more flexible in creating novel designs. One patient actually drew the same or very similar figure 61 times. These authors concluded that right hemisphere prefrontal functioning is impaired in schizophrenia.

Schizophrenics also demonstrate problems inhibiting inappropriate responses on the Stroop Interference Task (Beech, Powell, McWilliam, & Claridge, 1989; Goldberg et al., 1990; Liddle & Morris, 1991). Goldberg and colleagues found that, in addition to diffuse cognitive deficits, schizophrenics twins were differentially more impaired on this task compared to their non-affected twins.

Beech et al. (1991) used a variation of the Stroop paradigm to investigate selective attention in schizophrenia. They found that when a distractor that was previously ignored is re-presented there is an increased reaction time for normal subjects but not schizophrenics. They concluded that schizophrenia results in premature release from cognitive inhibition.

Schizophrenics are also noted to be impaired on other tests that tap prefrontal functions. For instance, they make more errors on the Continuous Performance Test (CPT), which requires sustained attention, short term memory, and inhibition of inappropriate responses (Gold & Harvey, 1993; Seidman et al., 1994). They require many more trials than controls to complete the Tower of Hanoi puzzle, which tests planning and problem solving abilities (Goldberg & Weinberger, 1988). They have also been found to be impaired on tests of left/right orientation and immediate memory for tactile spatial information (Malec, 1978; Kolb & Wishaw, 1983).

Some researchers have attempted to test more specific functions of the prefrontal cortex by using experimental paradigms that have been used in cognitive and physiological psychology research. Schizophrenics have been found to be impaired on tasks that require actively maintaining representations in short term memory (i.e., working memory) and other tasks that are sensitive to dorsolateral prefrontal damage (Park & O'Driscoll, in press; Park & Holzman, 1992, 1993; Spitzer, 1993; Goldberg et al., 1990). On an oculomotor DR task similar to one used with monkeys (Funahashi et al., 1989), schizophrenics are less accurate and slower in responding than controls (Park & Holtzman, 1992, 1993). They are also impaired on a version of the task that requires manual responding (Spitzer, 1993). Furthermore, Park and Holtzman (1992) demonstrated that poor performance on spatial delayed response was independent of modality because schizophrenics were equally impaired on a haptic version of the task. Sullivan et al. (1994) found schizophrenic patients to be impaired on a modified version of Petrides and Milner's (1982) nonverbal self-ordered pointing task relative to normal controls.

Although many researchers report prefrontal dysfunction in schizophrenia, not all patients fall within the impaired range on neuropsychological tests. Although, as a group, they tend to perform more poorly than normal controls, individual patients may perform within normal limits or even above the normal mean. The study by Goldberg et al. (1990) is important in this regard. These authors studied monozygotic twins discordant for schizophrenia and found that less than half of the schizophrenic patients scored below the *range* of performance of the group of unaffected twins. However, more than 75 percent of the schizophrenic twins performed worse than their unaffected twin on COWA and the WCST, suggesting a relative impairment of DLPFC functions.

Attentional problems are often seen in schizophrenia, including impaired selective attention, impaired sustained attention, and reduced speed of cognitive processing (Harness, Benthal, & Carmon, 1977; Goldberg et al., 1990; Gold & Harvey, 1993). Memory problems, as seen in patients with temporal lobe and/or diencephalic lesions (Bauer et al., 1993), also are common. Schizophrenics are often impaired on verbal paired associate learning, memory for passages, memory for drawings, and verbal list learning (Cutting, 1979; Gold et al., 1992; Goldberg et al., 1990; Holland, 1974; Kolb &

Wishaw, 1983; Saykin et al., 1991; Sullivan et al., 1994). In fact, Goldberg et al. (1990) showed that, on average, schizophrenic twins scored 23 points lower than their unaffected twins on the Wechsler Memory Scale (WMS) and Gold (1992) reported that thirty percent of his group of schizophrenics showed a greater than 15 point discrepancy between their own IQ scores and WMS performance.

There is some evidence that schizophrenics have impairments of manual dexterity and motor speed (Saykin et al., 1991). It is well known that they have abnormal eye-tracking abilities (Lieberman et al., 1993; Thaker et al., 1989; Park & Holzman, 1993).

In summary, schizophrenics demonstrate a wide range of cognitive deficits, with the greatest impairments seen on tests sensitive to prefrontal and limbic damage. It is important to keep all of these cognitive deficits in mind when we explore performance on neuropsychological tests. Performance on visuo-spatial tests may be impaired due to abnormal eye-tracking rather than defective visuo-spatial analysis, per se. Proper control tasks or statistical analyses that control for additional sources of variance are necessary in order to tease out the contributions of other cognitive deficits to the function(s) of interest.

Correspondence of Schizophrenic Symptoms and Cognitive Performance

Negative symptoms in schizophrenia have long been associated with poor performance on a range of cognitive tests (Strauss et al., 1974; Crow, 1980). They have also been found to be associated with poor premorbid functioning, poor prognosis, poor response to neuroleptics, and enlarged ventricles (Andreasen & Olsen, 1982; Andreasen, Olsen, Dennert, & Smith, 1982, Angrist et al., 1980, Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990, Crow, 1980, Johnstone et al., 1978, Strauss et al., 1974, Wolkin et al., 1992). In contrast, positive symptoms have been associated with a better prognosis, good response to neuroleptics, and minimal cognitive dysfunction (Angrist et al., 1980, Johnstone et al., 1978, Strauss et al., 1974). Correspondence between specific symptoms of schizophrenia and dysfunction of distinct brain regions have been reported by several investigators (Frith et al., 1991c, Liddle, Frith, et al., 1992, Stolar et al., 1994, Wolkin et al., 1992).

Poor performance on COWA and WCST tasks has been correlated with severity of a negative symptom complex including affective flattening, poverty of speech, and poverty of movement (Liddle & Morris, 1991, Stolar et al., 1994). That is, patients with negative symptoms also tend to be impaired on COWA. Stolar et al. (1994) found that the symptom of alogia was negatively correlated with performance on both design fluency and COWA, while affective flattening was negatively related to performance only on the design fluency task. They concluded that alogia is associated with bilateral DLPFC dysfunction while affective flattening is lateralized to right DLPFC. In their study, the specificity of the negative-symptom/DLPFC relationship was further highlighted by the findings that positive symptoms were not correlated with performance on either task and negative symptoms were not related to performance on other neuropsychological tasks.

One group of researchers examined the relationships between positive and negative symptoms, stability of symptoms, and performance on a spatial working memory task in a group of acutely ill schizophrenics (Park et al., in press). They found that negative symptoms remained stable over a two to two and a half week period, while positive symptoms improved significantly. Schizophrenics demonstrated impaired spatial working memory which, like the negative symptoms, did not improve over time. Working memory did not significantly correlate with the symptoms during the initial testing, although on the second testing day (at least two weeks later), there was an association of working memory and negative symptoms scores: those patients with more negative symptoms tended to perform worse on the working memory task.

Negative symptoms may occur in other psychiatric disorders other than schizophrenia, such as depression. If it is the negative symptoms, and not schizophrenia, per se, that are related to DLPFC dysfunction, we would expect to find DLPFC involvement in some depressed patients as well. Lodewyk and Wong (1993) found depressed patients to be impaired on COWA and verbal abstraction, which are both sensitive to left prefrontal dysfunction. Furthermore, depressed patients with poverty of speech demonstrate the same pattern of resting hypofrontality on PET imaging as schizophrenics with this symptom (Dolan et al., 1993). Depressed mood did not contribute to this effect.

Qualitative aspects of performance on a categorical version COWA may distinguish between two syndromes of schizophrenia (Allen et al., 1993). Patients with poverty of speech produce fewer words than controls while patients with thought disorder not only produce fewer appropriate words, they produce significantly more inappropriate words than controls and negative symptom patients. Similar patterns of performance are seen in neurologic patients with medial/subcortical and orbitofrontal damage, respectively, indirectly suggesting a possible relationship between these regions and negative and disorganization symptoms (Crowe, 1992). The disorganization syndrome (i.e. thought disorder and inappropriate affect) has also been associated with impaired performance on other tasks that require inhibition of inappropriate responses (i.e. Stroop Color Naming, Trail Making Test B; Dolan et al., 1993).

In summary, there is some behavioral and cognitive evidence that the prefrontal cortex may be involved in producing the negative symptoms of schizophrenia. Whether or not patients with negative symptoms actually have damage to the DLPFC can only be answered with imaging and physiological techniques. The following section reviews some of the neuroanatomical and metabolic findings of patients with schizophrenia. Since the majority of studies have explored schizophrenia as a unitary phenomenon, we first discuss the neuropathologic findings for schizophrenia as a single disorder. Then the relationship between regional brain abnormalities and the negative symptoms are reviewed.

Brain Pathology in Schizophrenia

Structural Brain Abnormalities in Schizophrenia

Postmortem studies provide evidence for decreases in brain weight, cerebral volume, and ventricular enlargement in schizophrenic patients (Dunlap, 1924; Bogerts et al., 1985; Brown et al., 1986; Gur et al., 1994). There have also been reports of decreased cell count in the cerebral cortex of schizophrenics (Miyakawa et al., 1972; Colon, 1972).

Computed tomography (CT) studies have consistently shown lateral ventricular enlargement (Johnstone, Crow, Frith, Husband, & Kreel, 1976; Johnstone et al., 1978). To control for possible reductions in total brain size, a common measure of ventricular size is the ventricular brain ratio (VBR). Schizophrenics have enlarged VBRs compared to normal controls (Andreasen et al., 1982; DeLisi, Goldin, Hamovit, Maxwell, Kurtz, & Gershon, 1986). In his review of the CT literature, Cannon (1994) stated that approximately three fourths of the CT studies looking and VBRs in schizophrenia demonstrated a significant degree of ventricular enlargement in patients as compared to non-psychiatric controls while one fourth report negative findings. There is some evidence that increased VBRs are greater in female patients and in the left hemisphere (Harvey et al., 1993). Investigations of the third ventricle are not as common but have demonstrated enlargement in schizophrenic patients (Cannon, 1994).

MRI studies have generally been consistent with CT and postmortem studies in demonstrating smaller overall cerebral volume and enlargements of the ventricles in schizophrenics compared to normal controls (Gur, 1992; Gur et al., 1994; Andreasen et al., 1986; Schaepfer et al., 1994; Zipursky et al., 1994).

Another indicator of relative loss of brain tissue in schizophrenia is the presence of widened cortical sulci. Cannon (1994) reported that approximately 2/3 of published CT studies found evidence of enlarged sulci in schizophrenia. Despite failure to find enlargement of lateral ventricles, in a group of unmedicated schizophrenics, Rubin et al. (1993) found sulcal enlargement in the Sylvian and interhemispheric fissures as well as in frontal and parietal regions. This was more pronounced in male patients and in the left hemisphere. Increased sulcal fluid has also been found with MRI (Harvey et al., 1993).

Studies exploring prefrontal anatomy have been inconsistent. Benes and her colleagues have conducted a series of postmortem studies examining the nature of the cellular pathology in schizophrenia (Benes, Davidson, & Bird, 1986; Benes, 1993; Benes et al., 1991). In one study, they discovered that neuronal density was lower in the layer VI of the prefrontal, layer V of the cingulate, layer III of the motor cortex, and most layers of the premotor cortex of schizophrenics compared to normal controls. Moreover, there were no differences between the ratio of neurons to glial cells in the two groups. These findings argue against a degeneration hypothesis, which would predict a higher ratio of glial cells. They suggest that the neuropathology of schizophrenia is at the level of cytoarchitectural variations possibly occurring in the early stages of development. In a later study, Benes et al. (1991) found that decreases in prefrontal neuronal density seem to be attributed to low levels of small interneurons, rather than fewer large pyramidal cells. Rajkowska, Selemon, and Goldman-Rakic (1994), also reported prefrontal abnormalities at the cellular level. However, rather than decreased neuronal density, they found that schizophrenic patients had fewer large pyramidal neurons and more medium and small neurons in the prefrontal cortex than normal controls (Selemon et al., 1995).

Due to poor resolution, few CT studies look at differences in specific cortical regions. Nonetheless, evidence from one CT study suggests that schizophrenics have decreased tissue density in the left frontal area (Golden et al., 1981) and that ventricular enlargement is more extreme in the frontal horns of the lateral ventricles (Schröder, Geider, & Sauer, 1993).

The application of MRI is a more sensitive technique than CT for examining sulcal changes and it permits visualization of specific cortical and subcortical structures. The advantages of MRI include better resolution, higher sensitivity to soft tissue contrast, the capacity to view the brain in three dimensions, no bone artifact, and no ionizing radiation (Gur, 1992).

The prefrontal region has been implicated in some, but not all, MRI studies of schizophrenia. Interest in this region stems from the abundance of neuropsychological and metabolic findings implicating frontal lobe dysfunction in schizophrenia. Andreasen et al. (1986) evaluated 38 schizophrenics and 48 controls and measured cranial area, cerebral area, frontal area, and ventricular brain ratios. They reported that patients had larger VBRs, smaller frontal lobes, and smaller cerebrums as well as craniums. In a second study (Andreasen et al., 1990) they did not replicate their findings of decreased cranial, cerebral, and frontal lobe size. In fact, these measures were slightly larger in the patient group, especially for the male subjects. The primary difference between these two studies was that in the first study the control subjects were hospital employees with higher educational levels than the patient group, while patient educational level was controlled in the second study. They concluded that the prefrontal differences in their 1986 study were probably related to educational differences, not schizophrenia. The authors recommended matching patients and normal controls for level of education and socioeconomic status in future studies. Others argue that an appropriate matching variable is parental socioeconomic and/or educational status because the schizophrenics disease state may actually interfere with their level of achievement (Gur et al., 1991). This seems appropriate if we want to ask the question, "Given a similar home environment, what distinguishes schizophrenics from non-schizophrenic individuals?" as opposed to the question "Given similar achievements, what distinguishes these groups?"

Thus, it could be argued that the control group in the the study by Andreasen et al (1990) was not appropriate. Matching on parental SES, Harvey et al. (1993) found reduced frontal volumes compared to controls. Similarly, Andreasen and her colleagues recently found that when they controlled for parental social class, frontal lobe volumes were differentially reduced in schizophrenics compared to controls (Andreasen et al., in press- neuroscience conference).

Another group of investigators using MRI with schizophrenics found reduced cortical grey in the DLPFC and other heteromodal association areas (e.g. inferior parietal lobule; Schlaepfer et al., 1994). These volume reductions were regionally specific in that no group differences were seen in occipital and sensory-motor areas. Controlling for temporal lobe size, Raine et al. (1992) also found smaller prefrontal areas in schizophrenic patients compared to controls. Reduced prefrontal white matter (Breier et al., 1992) and lack of normal rightward asymmetry of the prefrontal region have been reported (Bilder et al., 1994).

Others have failed to demonstrate structural abnormalities specific to the frontal lobes in schizophrenia (Kelsoe et al., 1988; Suddath et al., 1989; Andreasen et al., 1990; Young et al., 1991). Kelsoe et al. (1988) examined frontal lobe, temporal lobe, lateral and third ventricles, the amygdala hippocampal complex, and hemispheric volumes in 14 patients with schizophrenia. While third and lateral ventricle enlargement was seen in schizophrenics these authors could not identify localized tissue abnormalities. Wible and her colleagues recently reported no differences in prefrontal grey or white matter volumes between a group of primarily positive symptom schizophrenics and normal controls (Wible et al., 1995).

Some potential reasons for these inconsistent findings are differences in brain measures and patient populations. In some of the studies that have reported negative findings the frontal lobes or prefrontal region are often defined as all brain matter anterior to the genu of the corpus callosum (or some other landmark) and may involve only a single brain slice (Andreasen et al., 1986, 1990, Wible et al. 1995). It is possible that these definitions are not specific enough to reveal more subtle abnormalities within sub-regions of the prefrontal area. One study that used gross measurements of the DLPFC volumes reported decreases in that area (Schlaepfer et al. 1994). However, differences in prefrontal definition alone is not enough to explain the inconsistencies because some of the studies with positive findings used the same definition (i.e. everything anterior to the corpus callosum).

Another methodological issue is choice of participants. For example, Wible et al (1995) used a group of patients with primarily positive symptoms, while others may not have. Unfortunately, unless the researchers are specifically looking at symptoms in their analyses, they rarely report the types of symptoms displayed by their participants. This leads to the problem mentioned earlier of the heterogeneity of schizophrenic symptoms

As a single group, schizophrenics may include some patients with negative symptoms and some without. If only some of the symptoms of schizophrenia involve prefrontal cortex the variability within the group would reduce our ability to detect brain abnormalities that accompany specific symptoms of schizophrenia.

Functional Imaging in Schizophrenia.

In addition to investigations of structural abnormalities in schizophrenia, there is a growing body of literature of cerebral blood flow and cerebral metabolism studies also looking for possible neuropathologic contribution to the disease. These methods allow measurement of the metabolic activities and neurochemical properties of brain regions in conscious behaving human beings.

Ingvar and Franzen (1974) were among the first to identify regional differences in cerebral blood flow in schizophrenia compared to neurologically healthy controls. They found that schizophrenia was associated with decreased resting regional cerebral blood flow (rCBF) to the frontal cortex and increased flow to the postcentral cortex.

Poor performance on the WCST, a test sensitive to prefrontal damage, is associated with lower regional cerebral blood flow in the prefrontal cortex of schizophrenic patients compared to normal performance in normal controls (Weinberger et al., 1992; Berman, Torrey, Daniel, & Weinberger, 1992; Robin et al., 1994). A recent PET study by Weinberger et al. (1992) is particularly important because the subjects involved were twins who were discordant for schizophrenia. They found that, during activation (i.e. performance of the WCST), all of the affected twins were *hypofrontal*, i.e.

metabolism was lower than in normal controls, but not necessarily lower than baseline compared to their non-affected twins. In the affected twins, but not in the unaffected twins, prefrontal activation was strongly and negatively related to both left and right hippocampal volumes, suggesting that these regions may be different parts of the same network that is impaired in schizophrenia. Further supporting hypometabolism in the prefrontal cortex is the finding that drug naive schizophrenics have lower levels of adenosine phosphate and inorganic orthophosphate than normal controls in the DLPFC region (Pettegrew et al., 1991).

Others have failed to find "hypofrontality" associated with schizophrenia (Early et al., 1987). Early and colleagues examined unmedicated schizophrenics and did not find evidence of hypofrontality. They concluded that the so called hypofrontality reported by others is probably an effect of medication. However, positive findings reported for drug naive schizophrenics or those taking medication "holidays" along with positive results from studies that have statistically controlled for the effects of medication argue against this hypothesis (Bushbaum et al., 1982; Pettegrew et al., 1991; Dolan et al., 1993). Weinberger (1993) suggests that the conflicting findings are actually due to differences in methodology. Those that report negative findings (e.g. Early et al., 1987) measure metabolism or rCBF at rest rather than during tasks that require the integrity of the DLPFC. It may be that in order to demonstrate abnormal functioning in a certain brain region it is necessary to tax that area cognitively.

Thus, finding from PET studies provide some of the strongest evidence of prefrontal involvement in schizophrenia. There is also some evidence from PET studies that abnormalities with DLPFC may be specifically involved in producing some of the negative symptoms (Dolan et al., 1993; Wolkin et al., 1992; Hemmingsen et al., 1994). The relationship of specific negative and positive symptoms to regional structural and functional brain abnormalities will be discussed next.

Relationship of Specific Symptoms to Regional Brain Abnormalities

If negative symptoms are indeed the result of cognitive impairment involving DLPFC, we would expect to see a positive relationship between pathology of the DLPFC (or systems involving DLPFC) and the severity of negative symptoms. Correspondence between specific symptoms and anatomic and functional abnormalities have been reported by several investigators. There is substantial evidence that the negative symptoms of schizophrenia are related to various brain abnormalities. The question of whether these are regionally specific or generalized remains controversial. The findings regarding positive symptoms have tended to be more regionally specific.

Ventricular enlargement, particularly within the frontal horns, has frequently been associated with negative symptoms (Andreasen et al., 1982; Andreasen & Olsen, 1982; Andreasen et al., 1990). Increased ventricular size in schizophrenia is also associated with general cognitive impairment (Johnstone et al., 1976; Johnstone et al., 1978; Andreasen et al., 1982). Keilp et al. (1988) found that, with their group of schizophrenics, enlargement of the frontal horns of the lateral ventricles was related to intellectual deficits, problems with conceptual thinking, immediate verbal memory, and psychomotor speed. The size of the body of the lateral ventricles was positively correlated with psychomotor speed and negatively correlated with immediate verbal memory. Severity of negative symptomatology also was negatively correlated with measures of psychomotor speed and alternation (i.e. Tapping, Trails B), but not ventricle size.

Increased sulcal cerebrospinal fluid, decreased total brain size, and smaller intracranial volumes also have been found to be related to negative symptoms (Andreasen et al., 1982; Gur et al., 1994). Andreasen's group found that negative symptoms (i.e. alogia, affective blunting, avolition, anhedonia, and attentional impairment) were associated with decreased cerebral and cranial size. In addition, poor performance on cognitive tests sensitive to frontal lobe damage (i.e. WCST, Stroop, COWA) were associated with decreased cranial and cerebral size, but not frontal size.

A relationship between negative symptoms and structural and functional abnormalities of the DLPFC has been implicated by some investigators. Negative symptoms have been associated with decreased glucose metabolism in the DLPFC (Dolan et al., 1993; Wolkin et al., 1992; Hemmingsen et al., 1994). However, in two studies that also looked at anatomical data, there was no evidence of corresponding structural abnormalities in the total prefrontal region (Wolkin et al., 1992; Hemmingsen et al., 1994). In an MRI study, severity of negative symptoms in a group of chronic schizophrenics was related to higher left frontal temporal T2 ratios indicating possible left prefrontal tissue pathology (Williamson, Selz, Merskey, Morrison, & Conlon, 1991).

Contradictory findings also have been reported. Raine et al. (1992) found no correspondence between the size of prefrontal areas (MRI area measures of single slices in three planes) and symptom type or severity. Additionally, performance on neuropsychological measures of prefrontal functions were not associated with prefrontal size. Buchanan and his colleagues found that patients with a *nondeficit syndrome* (i.e. lack of negative symptoms) have smaller prefrontal volumes than those with *deficit syndrome*, i.e., those with enduring negative symptomatology (Buchanan et al., 1993).

Buchanan et al. (1993) also found that size of the caudate nucleus differentiated schizophrenics with negative symptoms from those with positive symptoms. Both deficit and nondeficit groups has enlarged left caudate nuclei. However, deficit patients differed from nondeficit patients and normal controls in that their caudate nuclei were symmetrical, while the other groups had larger right than left caudate nuclei. This finding is complicated by results from another group of investigators that found bilateral decreases in caudate volumes in patients with negative symptoms (Young et al., 1991). However, the latter authors used eight mm brain sections, compared to three mm slices used by the former, which may have resulted in error due to partial volume averaging in a structure as small as the caudate.

In conflict with evidence that negative symptoms are associated with ventricular enlargement, data has been reported suggesting that patients with positive symptoms have larger VBRs than patients with negative symptoms and normal controls (Young et al., 1991). Still others have reported that increased VBRs were associated with severity of both positive and negative symptoms (Gur et al., 1994).

The positive symptom, severity of auditory hallucinations, has been associated with decreased left temporal lobe and left superior temporal gyrus volumes ($r = .70$, Barta et al., 1990). Another group of researchers found that decreased volume of mesiotemporal structures was related to increased severity of positive symptoms, but not negative symptoms ($r = -.61$ and $r = .10$ respectively; Bogerts et al., 1993). There is further evidence of a relationship between positive symptoms and decreased glucose metabolism in temporal lobe auditory association cortices and Wernicke's region and increased activity in the striatum and anterior cingulate regions (Cleghorn et al., 1992). Hemmingsen et al. (1994) found increased glucose metabolism during performance of the WCST in the temporal cortex and striatum of patients with positive symptoms. In their sample, severity of positive symptoms correlated positively with size of the temporal horns. The left superior temporal gyrus has also been implicated in symptoms of thought disorder (Shenton et al., 1992).

In summary, the negative symptoms of schizophrenia are associated with nonspecific brain tissue volume decreases and there is minimal evidence that the negative symptoms are more specifically associated with prefrontal abnormalities. Although positive symptoms are not the focus of these thesis, it is noteworthy that positive symptoms have not been related to prefrontal volume, but instead have been associated with temporo-limbic structures, suggesting different underlying neuropathologies for the two symptoms clusters.

Models of Schizophrenia and Executive Functions

A number of models have been put forth to explain the mechanisms of schizophrenia. Drawing on evidence from cortical stimulation, neuroimaging, and postmortem studies, Weinberger's group (Weinberger et al., 1986; Weinberger & Berman, 1988; Weinberger, 1991) suggests that schizophrenia involves a subtle static brain lesion that interrupts connections between certain periventricular limbic nuclei and dorsolateral prefrontal cortex. This lesion would deafferent prefrontal cortex of its mesocortical dopaminergic innervation resulting in dopamine hypoactivity. This would explain the prefrontal hypometabolism seen in schizophrenia as well as the negative symptomatology. Conversely, positive symptoms are postulated to be caused from mesolimbic dopamine overactivity, possibly resulting from disrupted inhibitory feedback from prefrontal cortex to the ventral tegmental area (i.e., dopamine containing cells). This model suggests that cognitive and behavioral deficits seen in schizophrenia are not due to damage within the prefrontal cortex per se, but, rather, are a result of abnormal innervation of and feedback from this region. If this were the case, we would likely see both white matter loss and grey matter loss, due to anterograde and retrograde degeneration, in the DLPFC region. Whether or not these changes could be detected with current imaging techniques is not certain.

Goldman-Rakic (1991, 1994) postulates that "the most likely focus of a lesion in this disorder may be the cortico-cortical processing networks by which prefrontal cortex 'accesses' and holds 'on line' representational knowledge of the outside world through its connections with parietal and limbic centers" (1991, p. 17). She suggests that some of the positive symptoms are due to disruptions of prefrontal projections to both parietal and temporal association areas. These feedback projections probably gate sensory information that these areas receive from the thalamus and secondary sensory areas

Disruption of these projections may lead to altered consciousness of sensory experiences. On the other hand impairment of feed-forward projections to and from the prefrontal cortex may be important in producing some of the negative symptoms. Overall, the implication is that schizophrenia is a unitary disease process.

The Maryland Psychiatric Research Center (Breier et al., 1992; Breier, Davis, Buchanan, Moricle, & Munson, 1993; Buchanan et al., 1993) has been testing the hypothesis that the deficit syndrome of schizophrenia involves disruption of a prefrontal-subcortical circuit that was described by Alexander et al. (1986). As described earlier, this circuit is characterized by projections from the cortex to the caudate nucleus, from the caudate to the globus pallidus/substantia nigra, from these nuclei to the thalamus, and, to complete the circuit, projections from the thalamus back to the DLPFC. In support of their hypothesis, they have found that deficit patients had decreased white matter volumes in prefrontal regions and increased volumes of the caudate nuclei bilaterally. These finding were regionally specific to the extent that they did not find structural abnormalities in other brain areas (e.g. amygdala/hippocampal complex; Buchanan et al. 1993). However, they also found decreased prefrontal volumes and a lack of normal asymmetry of the caudate nuclei in nondeficit patients, suggesting that this circuit may be involved differentially in producing nondeficit symptoms as well.

In his book, The Cognitive Neuropsychology of Schizophrenia, Frith (1992) attempts to integrate evidence from neuropsychological investigations of schizophrenia, with neuroanatomical and cognitive models of brain processes. He proposes an information processing model to account for the various signs and symptoms of schizophrenia. Frith refers to observable behavioral abnormalities of schizophrenia as signs (i.e. flat affect, disorganized speech) and to experiential abnormalities as symptoms (e.g. hallucinations, delusions).

According to Frith's model, there are two routes to action. Some actions are carried out in response to environmental stimuli. Others are seemingly spontaneous and self initiated. For example, seeing a red light when driving elicits a stimulus driven response (i.e. stepping on the break). On the other hand, an individual may decide to stop the car based on internal goals, such as the desire to rest, in the absence of any external cues. Frith suggests that people with the negative symptoms of schizophrenia have problems with the latter type of action, which he calls the "willed route to action." This model is illustrated in Figure 1.

Frith suggests that schizophrenics with negative behavioral features are not able to translate their goals into intentions and subsequent actions. His model predicts that damage to the "willed route to action" would produce three possible outcomes: (1) the inability to initiate action, (2) the tendency to repeat a previous action or produce stereotyped automatic responding; (3) the production of inappropriate behavior in response to a stimulus in the environment.

The first prediction is supported by the observation that schizophrenics with negative symptoms demonstrate poverty of activity including poverty of speech, flattening of affect, and social withdrawal. Frith and his colleagues have conducted a number of studies in order to test this hypothesis further from a cognitive perspective. The primary supporting evidence for this prediction comes from the neuropsychological literature which indicates that schizophrenics as well as neurological patients with frontal lobe damage are impaired on COWA and design fluency (Kolb & Wishaw 1983, Stuss & Benson 1986 Lodewyk & Wong, 1993) In addition, Frith and his colleagues have conducted a series of studies demonstrating that negative symptoms are associated with poor performance on COWA and have linked this deficit to the dorsolateral frontal lobes primarily on the basis PET studies Although deficits on COWA may be the result of a depleted store of words in the lexicon problems may also result from an inability to perform a self-directed search. Given that schizophrenics perform relatively well on vocabulary tests, Frith suggests that their lexicon is intact, but that their ability to perform a self directed search is impaired (Frith 1992)

The second prediction, that people with a damaged "willed route to action" will demonstrate a tendency to repeat a previous action or produce stereotyped responses is supported by schizophrenics' tendency to perseverate on themes, words and actions spontaneously This prediction has been tested with a two choice guessing task, in which the subject was required to repeatedly guess whether the next card in a deck of playing cards would be red or black (Frith & Done, 1988). Schizophrenics had a tendency to produce predictable response sequences (e.g red, black, red, black or red, red, red, red) as opposed to normal controls who produced more random sequences of responses. This tendency to perseverate is also seen on other tests such as design fluency, and the WCST (Kolb & Wishaw 1983).

The third prediction, that problems with internal generation of responding will result in inappropriate responses to stimuli in the environment, is based on the idea that the stimulus driven route to action is still intact According to Frith, incoherence of

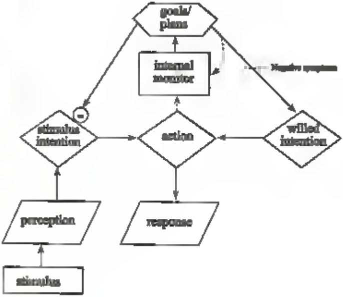
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Figure 1. Frith's information processing model of schizophrenia
Negative symptoms result from a disconnection between goals and intention

speech, loose associations, clanging and incongruity of affect are examples of this problem. He suggests that poor performance by schizophrenic subjects on the Stroop Interference Test supports this prediction. On this task, schizophrenics, as well as neurological patients with frontal lobe damage have difficulty inhibiting their response to the written word. Furthermore, Liddle and Morris (1991) found that incongruity and incoherence were associated with poor performance on the Stroop.

Frith's model also accounts for experiential symptoms of schizophrenia such as hallucinations and delusions (Frith, 1992). He states that normally, we monitor our own thoughts, efforts and actions. Schizophrenics with positive symptoms have problems with their internal monitor. As a result, they perceive their thoughts and actions as initiated by external agents. In addition, attempts to place meaning on their experiences may lead to delusions. A review of the literature supporting this aspect of Frith's model is beyond the scope of this paper. It is mentioned primarily to note that his model attempts to account for both positive and negative signs and symptoms of schizophrenia.

Frith's (1992) model is consistent with Shallice's (1988) Supervisory Attentional System (SAS), which was put forth to describe automatic versus consciously selected action, which he suggests is mediated by the frontal lobes. This distinction is illustrated by normal occasional "lapses in action" which are referred to as *capture errors*. For example, you may be driving to a party, when suddenly, you realize that you are driving toward your work place, simply out of habit. Most people make capture errors on occassion.

There are two premises to Shallice's model: (1) routine selection of routine operations is automatic, (2) nonroutine selection of actions is qualitatively different and requires a supervisory "executive" system. This model is illustrated in Figure 2. Shallice suggests that we possess core programs for actions which can be elicited automatically and with little effort. These programs are triggered by environmental stimuli. The available programs compete, or "contend," with each other through a process of mutual inhibition. The most highly activated schemata is ultimately implemented, while the others are suppressed. This process occurs within what Shallice refers to as the *contention scheduling system*.

While the contention scheduling system is able to operate on its own, for normal behavior to occur, it requires some kind of supervisory system that executes plans, provides input on internal motives, and learns from its mistakes. Shallice refers to this executive system as the *Supervisory Attentional System* (SAS). If, for example, an alarm clock rings and wakes you up in the morning, the automatic response may be to press "snooze." However, pressing snooze is simply the default response. Internal motivations and plans may lead the SAS to overrule the "snooze" response and trigger the "get up" response.

According to Shallice, capture errors are momentary lapses of the SAS that result in stimulus driven behavior that is inappropriate to the situation. In addition, he suggests that patients with frontal lobe damage have a dysfunction of the SAS. That is, while

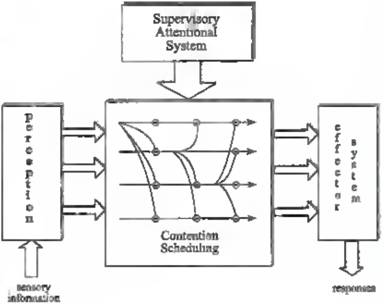
Supervisory Attentional System
perception
Contention Scheduling
effector system
sensory information
responses

Figure 2. Shallice's (1988) Supervisory Attentional System

contention scheduling is initiated through environmental triggers, there is little internal or "willed" modulation of what programs are ultimately chosen. This is very similar to Frith's (1992) model depicting alternative "willed" and "stimulus-driven" routes to action.

Both schizophrenic patients and individuals with prefrontal damage share the behavioral features of difficulty in initiating activity, problems planning and realizing goals, an over reliance on prepotent responses, and inappropriate responding to stimuli in the environment. Shallice interprets the poor performance of frontal patients on the WCST as reflecting dysfunction of the SAS. He suggests that with an impaired SAS, if on one trial, a particular schema is strongly activated by a stimulus trigger, the contention scheduling system, when faced with the same environmental triggers, will continue to select that schema on subsequent trials regardless of the feedback that occurs. Thus, the problems that frontal lobe patients and schizophrenics demonstrate in switching strategies and perseverating on incorrect responses despite feedback, may be viewed as an impairment of the SAS. A study by Verin et al. (1993) is consistent with Shallice's idea of an impaired SAS. These authors found that, using a delayed response paradigm, patients with DLPFC damage automatically chose an alternating pattern of responding, rather than testing alternative strategies; they may have relied on a preprogrammed sets of responses.

When there are no strong stimulus triggers in the environment, contention scheduling may be easily influenced by irrelevant stimuli. Shallice suggests that the utilization behavior described by Lhermitte (1983) is an example of this. A dysfunction of the SAS presents particular problems in novel situations as it is unlikely that an existing subroutines in contention scheduling will be appropriate to deal with the situation. Shallice (1988) suggests that this problem of dealing with new situations can be illustrated with problem solving tasks, such as the Tower of London. Patients with left frontal damage are particularly impaired on this task, which requires substantial planning ability.

Both Frith's (1992) and Shallice's (1988) models suggest that goals, plans, strategies, and correction of responses based on feedback are mediated by the frontal lobes, but that execution of the actual motor response is mediated through subcortical and cortical motor systems. Frith (1992) noted the parallels between these cognitive models and the corticostriatal loops described by Alexander et al. (1986). He stated that the SAS are likely to involve the dorsolateral prefrontal cortex, anterior cingulate cortex and the supplementary motor area, while contention scheduling probably occurs in subcortical structures including the basal ganglia. This is consistent with Penney and Young's (1986) accounts of the subcortical motor diseases, Huntington's Chorea and Parkinson's disease. They describe the role of the basal ganglia, subthalamic nucleus, and substantia nigra in the selection and maintenance of wanted movements and in the inhibition of unwanted movements.

Although Parkinson's disease is caused by subcortical pathology, some of the behavioral features are similar to those demonstrated by frontal lobe patients (e.g., poverty of speech and poverty of movement). However, Parkinson's patients can be differentiated from frontal lobe patients because the problem is more one of initiating a motor response, while the frontal lobe patient is able to respond motorically, but has trouble translating goals and intentions into motor responses.

All of the above models of schizophrenia involve dysfunction of a brain network that involves the DLPFC. However, because of the lack of strong evidence of structural abnormalities in the prefrontal region many investigators have assumed that the abnormality is not in the prefrontal cortex, per se, but rather, in other areas that have connections with the prefrontal cortex. While this is a tenable hypothesis, given the wealth of neuropsychological and PET data implicating the DLPFC, it seems premature to stop looking within the prefrontal cortex. As already discussed, there are several potential reasons for the conflicting evidence regarding the relationship of the DLPFC and schizophrenia of which the heterogeneity of symptoms and measurement techniques are probably amongst the largest contributors. In the present study we dealt with the problem of heterogeneity by focusing on specific symptoms of schizophrenia rather than looking at schizophrenics as a homogeneous group. Furthermore, rather than measuring the prefrontal cortex as whole, we looked specifically at a subregion of the DLPFC, namely area 46. By measuring the entire prefrontal cortex, previous studies may have inadvertently "washed out" potentially relevant relationships between particular subdivisions of the prefrontal cortex and specific symptoms of schizophrenia. One reason that previous investigations have not measured the subdivisions of the prefrontal cortex is that these regions are defined according to cytoarchitecture. Therefore, their boundaries cannot be identified on MRI or CT. We have identified a region within the DLPFC as a decent approximation of area 46 (area 46,) based on available cytoarchitectonic and functional imaging data. This region can be identified on MRI on the basis of morphologic landmarks and stereotaxic coordinates (Talairach & Tournoux

1988). Focusing on area 46, alleviates the problem of heterogeneity of pathology within the prefrontal cortex and will help clarify the role, if any, of this region in the negative symptomatology of schizophrenia.

Rationale of Study and Hypotheses

This project was motivated by the knowledge that prefrontal lesions in humans and primates lead to behavioral deficits that closely resemble the negative symptoms and cognitive deficits of schizophrenia. A review of the findings from neuropsychological, neurophysiology, and neuroanatomic studies point to the dorsolateral prefrontal area as being crucial for guiding behavior based on internal representations or working memory. Our working hypotheses was that area 46, in the dorsolateral prefrontal cortex is involved in the negative symptoms of schizophrenia. In order to challenge this general hypothesis, we examined area 46, in schizophrenic patients and controls two ways. First, we investigated the functional integrity of this region by measuring cognitive functions (i.e. working memory) that have been found to be specifically associated with this region in humans and nonhuman primates. Second, we examined the structural integrity of this region by measuring its relative volume on MRI scans. We then explored the relationships between negative symptoms and both structural and cognitive measures. The following specific questions and hypothesis were addressed. Is working memory related to negative symptoms? Is the size of area 46, related to negative symptoms? Are there group differences between schizophrenics and controls that reflect an underlying process that is common to all forms of schizophrenia?

Is Working Memory Performance Related to Negative Symptoms? We addressed this question by examining the relationship between negative symptoms and performance on two working memory tests. The spatial delayed response task (SDRT) (Park & Holzman, 1992; Spitzer, 1993) and the self-ordered pointing (SOP; Petrides & Milner, 1985) were used because they have been relatively well localized to area 46 in nonhuman primate with lesion and single cell recording studies (Goldman-Rakic, 1987) and in humans with functional imaging studies (Jonides et al., 1993). We predicted that performance on the SDRT and SOP tasks would be predictive of negative symptomatology. In order to test the hypothesis that damage to area 46 is selectively involved in producing the negative symptoms and that negative symptoms can not be accounted for by diffuse brain dysfunction, the Wechsler Adult Intelligence Scale Revised (Wechsler, 1981) was administered to all participants. Additionally, a control task, phonemic discrimination, was administered in order to further test the specificity of any working memory/negative symptom associations. While the phonemic discrimination may be abnormal in a subgroup of schizophrenics, there is no direct evidence to suggest that it is related to the negative symptoms of schizophrenia. Finally, the specificity of the negative symptom/working memory association can only be established if working memory performance is not predictive of positive or disorganized symptoms. Therefore, the relationships between working memory and these symptom clusters also were examined. The following specific hypotheses were made

1. Increased errors on the SDRT and SOP tasks will be associated with greater severity of negative symptoms
2. Increased errors on the control task (i e phonemic discrimination) will not be associated with greater severity of negative symptoms.
3. The relationship between working memory performance and negative symptoms will not be accounted for by global cognitive decline That is working memory performance will have greater value than IQ in predicting negative symptoms
4. Increased errors on the SDRT and SOP tasks will not be associated with severity of positive or disorganized symptoms

Is the Size of Area 46_r *Related to Negative Symptoms?* This question was addressed by measuring area 46_r volumetrically on MRI scans. We predicted that smaller area 46_r volumes would be associated with more severe negative symptoms and that this would not be accounted for by smaller total brain volumes. As with the cognitive measures, the specificity of this relationship was further examined by looking at a control brain region (i.e. planum temporale) thought to be unrelated to area 46_r. This region is contains auditory association cortex and therefore may be involved in phonemic discrimination, our control task Some authors have reported abnormal assymetry of the planum in schizophrenics (Petty et al 1995); however there is no evidence to suggest that pathology in this brain region is associated with negative symptoms Therefore, we predicted that the size of the planum temporale would not be associated with negative symptoms. Finally, it was predicted that the size of area 46_v would not be associated with positive or disorganized symptoms. Specific hypotheses are as follows:

5. Smaller area 46_v volumes, controlling for total brain volumes, will be associated with greater severity of negative symptoms.
6. Smaller size of the control brain region (i.e. planum temporale) will not be associated with greater severity of negative symptoms.
7. Total brain volumes will not be predictive of negative symptomatology.
8. Area 46_v volumes will not be associated with severity of positive or disorganized symptoms.

Are there group differences between schizophrenic patients and controls that may reflect an underlying process that is common to all forms of schizophrenia? This question is of exploratory nature, because, as previously addressed, schizophrenics are a heterogenous group and the purpose of this study was to examine the relationships between specific symptoms and regional brain pathology. Nonetheless, group differences were explored in order to assess the consistency between the current findings and other studies. Moreover, examining group differences allows us to remain open to the possibility that, despite extreme heterogeneity of symptoms, there may be an underlying brain process that is common to all forms of schizophrenia.

METHODS

Participants

Patient Group

Twenty-three patients diagnosed with schizophrenia according to DSM-IV criteria by a board certified psychiatrist were recruited from psychiatric inpatient and outpatients services at the Veteran's Administration Medical Center and Shands Hospital in Gainesville Florida. A summary of demographic information is provided in Table 1. Length of illness (LOI) ranged from 10 to 40 years ($M = 22.86$, $SD = 8.75$) according to patient report and/or medical record documentation. Sub-diagnoses at the time of testing included 7 Undifferentiated, 13 Paranoid, and 3 Residual Type. All patients were receiving medications for treatment of their schizophrenia symptomatology (risperidone n = 10, clozapine, n = 2, Prolixin, n = 2, haloperidol, n = 4, Navane, n = 2) and some were recieving additional medication for other psychiatric symptoms (e.g. anxiety), side effects, and medical conditions (Cogentin, n=7, benzodiazapines, n=8, beta blockers, n=1, other n=13). The majority of patients ($n = 20$) were recieving outpatient care. Three patients were hospitalized on the psychiatric unit at the VA, but none was experiencing an acute psychotic episode at the time of testing. Inpatients were tested when they were stabilized (i.e., no longer experiencing acute psychosis), according to the psychiatrists' report and observation.

Table 1

Demographic Means

	Groups			
	Controls		Schizophrenics	
Variable	*M*	*SD*	*M*	*SD*
Age	43.26	9.58	46.47	4.24
Quantitative handedness	0.62	0.54	0.55	0.61
Parental SES	39.77	13.96	38.83	2.68
Height (in.)	71.77	2.85	70.14	3.33
Weight (lb.)	193.24	26.90	189.46	42.38
Length of illness (yrs)	–	–	22.86	8.75
Frequency of hospitalization	–	–	5.94	2.99

Note. Patients did not differ from controls on any of the demographic variables

Exclusionary criteria included any previous history of CNS illness, head injury leading to loss of consciousness for over 5 minutes, major medical conditions such as liver or heart disease, history of electroconvulsive therapy, and excessive use of alcohol, drugs, or steroids in the last 3 months. Because neuroimaging studies have identified differences between males and females in brain structures (Andreasen et al., 1986), and because the majority of these patients were recruited from the VA, the sample in the study was limited to males only.

Control Group

Twenty-three normal male controls were recruited from the community, University of Florida, and Shands Hospital with posted flyers. This group was balanced with the schizophrenic sample for age, quantitative handedness, parental socioeconomic status (SES), height, and weight (see Table 1). The procedure for calculating quantitative handedness and parental SES is described below in the Protocol section. Individual t-tests revealed no significant differences between the two groups on any of these variables. Exclusionary criteria for the NC group were identical to that of the SCZ group with the additional excusionary criterion of a positive history of psychiatric illness in themselves or a first degree relative.

Protocol

Interviews and Questionnaires

Demographics and information about the history and course of illnesses were gathered through screening questionnaires, medical records and interviews with patients and caretakers. Interviews were conducted by a psychiatrist (J.K.) or a clinical psychology graduate student (P.Z.). All participants completed an interview that included questions regarding family and personal psychiatric, neurological, medical, educational and employment histories. Quantitative handedness was measured with a questionnaire (Briggs & Nebes, 1974) that requires respondents to indicate degree of laterality for twelve specific activities (e.g. hand used to throw a ball, foot used to kick a ball, eye used to look through a camera) on a 5 point scale (-2 = always left, -1 = usually left, 0 = equally right and left, 1 usually right, 2 always right). Points from the 12 items were summed and divided by 24 (the number of possible points a consistently strongly right hander would obtain) This calculation yielded a quantitative "handedness" score ranging from -1 (strongly left side dominant) to +1 (strongly right side dominant) Parental SES was calculated using Hollingshead's four factor index of social status. Calculations are based on scaled score values assigned for level of education and occupation for each parent (see Eq 1) Computed

$$SES = [(5*OF + 3*EF) + (5*OM + 3*EM)] / 2 \qquad (1)$$

where

OF = scale value for occupation of father
EF = scale value of education for father
OM = scale value for occupation of mother
EM = scale value of education for mother

scores range from a high of 66 to a low of 8 The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) was administered to all participants in this study The interviews were videotaped for scoring symptoms as described below

Symptom Measurement

Symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS Kay, 1992) Ratings were made according to the participants' responses and behaviors during the SCI PANSS interview The PANSS provides reliable ratings of 30 symptoms which are divided into positive, negative and general psychopathology subscales. These contain measures of all the major psychotic symptom areas of interest except for inappropriate affect. Inappropriate affect was rated with a modified version of the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Extensive validity and reliability studies on the PANSS scales are reviewed in Kay (1992). With regard to reliability, Kay (1992) reported internal consistencies (alpha coefficients) within each scale ranging from .73 (positive symptoms) to .83 (negative symptoms). Test-retest reliability ranged from .77 (positive) to .89 (negative), and interrater reliability ranged from .83 (positive) to .87 (general psychopathology). With regard to validity, positive and negative symptom clusters were significantly correlated with positive and negative symptom scores on the Scale for Assesement of Positive Symptoms (r = .77) and the Scale for Assessment of Negative Symptoms (r= .77), respectively.

In the present study, three trained raters scored each participant on the 31 symptoms. Symptoms were grouped into clusters of Negative, Positive, Disorganized, and General Psychopathology symptoms as indicated below. Individual symptoms scores range from 1 (normal) to 7 (severe). When any of the three raters differed, by 2 or more points, from another rater on an individual symptom scale, the raters discussed the symptoms and a consensus score was used. An effort was made to conduct assessments during periods of relative stability (according to caretaker or health care staff reports) for the patients so that they were able to tolerate interviews and testing. Mean symptoms scores are provided in Table 2.

Table 2

Mean Symptom Scores from the PANSS and Abbreviated PANSS (A_PANSS)

	PANSS *n* = 23		A_PANSS *n* = 18	
Symptom/Cluster	*M*	*SD*	*M*	*SD*
Negative Symptoms (total)				
Schizophrenics	**21.70**	**6.00**	–	–
Controls	**7.75**	**0.85**	–	–
Blunted affect (N1)				
Schizophrenics	3.48	1.38	3.28	1.64
Controls	1.05	0.22	1.14	53
Emotional withdrawal (N2)				
Schizophrenics	3.48	1.63	2.50	1.38
Controls	1.00	0.00	1.07	27
Poor rapport (N3)				
Schizophrenics	3.57	1.12	–	–
Controls	1.05	0.22	–	–
Passive/apathetic social withdrawal (N4)				
Schizophrenics	3.44	1.59	2.89	1.60
Controls	1.05	0.22	1.00	0.00
Difficulty in abstract thinking (N5)				
Schizophrenics	3.52	1.18	–	–
Controls	1.60	0.82	–	–
Lack of spontaneity and flow of conversation (N6)				
Schizophrenics	2.35	1.56	2.44	1.58
Controls	1.00	0.00	1.14	0.53
Stereotyped thinking (N7)				
Schizophrenics	2.87	1.14	–	–
Controls	1.00	0.00	–	–

Note. Individual symptoms are rated on a scale from 1 (normal functioning) to 7 (severe symptomatology). Symptom cluster scores are identified in bold print.

Table 2 continued

	PANSS *n* = 23		A_PANSS *n* = 18	
Symptom/Cluster	*M*	*SD*	*M*	*SD*
Positive symptoms (total)				
Schizophrenics	**10.52**	**(6.31)**	–	–
Controls	**6.65**	0.99	–	–
Delusions (P1)				
Schizophrenics	4.48	1.88	3.61	1.53
Controls	1.00	0.00	1.00	0.00
Hallucinatory behavior (P3)				
Schizophrenics	3.61	1.73	2.11	1.57
Controls	1.00	0.00	1.00	0.00
Excitement (P4)				
Schizophrenics	1.44	0.95	–	–
Controls	1.05	0.22	–	–
Grandiosity (P5)				
Schizophrenics	2.87	1.74	–	–
Controls	1.15	0.49	–	–
Suspiciousness/ persecution (P6)				
Schizophrenics	4.13	1.46	–	–
Controls	1.30	0.47	–	–
Hostility (P7)				
Schizophrenics	2.00	1.13	–	–
Controls	1.15	0.49	–	–
Disorganized symptoms (total)				
Schizophrenics	**5.68**	**2.57**	–	–
Controls	**2.06**	**0.22**	–	–
Conceptual disorganization (P2)				
Schizophrenics	2.91	1.99	3.17	1.98
Controls	1.05	0.22	1.00	0.00
Inappropriate affect (P8)				
Schizophrenics	2.86	1.55	2.39	1.61
Controls	1.00	0.00	1.00	0.00

Note. Individual symptoms are rated on a scale from 1 (normal functioning) to 7 (severe symptomatology). Symptom cluster scores are identified in bold print

Table 2 continued

Symptom/Cluster	Schizophrenics *n* = 23		Controls *n* = 20	
	M	*SD*	*M*	*SD*
General psychopathology (total)	**41.17**	**8.46**	**18.99**	**2.65**
Somatic concerns (G1)	2.35	1.50	1.05	0.22
Anxiety (G2)	3.17	1.15	1.40	0.82
Guilt feelings (G3)	2.39	1.50	1.45	0.83
Tension (G4)	2.78	0.80	1.50	0.51
Mannerisms and posturing (G5)	2.17	1.30	1.00	0.00
Depression (G6)	3.35	1.15	1.45	0.89
Motor retardation (G7)	2.30	1.40	1.10	0.31
Uncooperativeness (G8)	1.65	0.89	1.00	0.00
Unusual thought content (G9)	3.13	1.33	1.20	0.52
Disorientation (G10)	1.91	0.95	1.10	0.31
Poor attention (G11)	1.91	1.10	1.00	0.00
Lack of judgment (G12)	3.78	1.16	1.05	0.22
Disturbance of volition (G13)	2.30	1.19	1.05	0.22
Poor impulse control (G14)	2.00	1.21	1.35	0.59
Preoccupation (G15)	2.61	1.00	1.10	0.31
Active social avoidance (G16)	3.35	1.50	1.10	0.31

Note. Individual symptoms are rated on a scale from 1 (normal functioning) to 7 (severe symptomatology). Symptom cluster scores are identified in bold print.

An abbreviated version of the PANSS was administered whenever a greater than one week delay occured between interview and testing in order to assess stability of symptoms. The abbreviated PANSS was composed of six symptoms selected from the PANSS (i.e., N1, N2, P3, P6, P2, P8) and included two symptoms from each symptom cluster. Mean scores from the abbreviated PANSS are provided in Table 2.

Measures of Cognitive Functions

Intellectual testing

To assess whether some clinical subjects have general intellectual deficits, such that poor performance on the neuropsychological tests would reflect poor overall mental ability rather than localized dysfunctions, subjects were administered the Wechsler Adult Intelligence Scale- Revised (WAIS-R; Wechsler, 1981).

Working memory

Two tasks were administered in order to examine the functional integrity of area 46: a spatial delayed response task (SDRT; Park & Holzman, 1993, Spitzer, 1993), and an abreviated version of Petrides & Milner's (1982) self-ordered pointing (SOP) task. In the sense that individuals are required to keep information in mind over a delay and generate a response based on an internal representation, both tasks require working memory. The difference is that the SDRT task relies on spatial working memory, while the SOP requires working memory for ones' own previous responses.

Spatial delayed response task. The stimulus material consisted of 16 white dots about 7 cm in diameter displayed on a black computer screen. Subjects were seated with their heads stabilized in a chin rest about 50 cm from the viewing screen. Stimulus presentation and data acquisition were controlled by an IBM compatible PC with an EDMARK TouchWindow® touch sensitive screen. Stimuli were presented on a 15 in monitor and the visual angle from the fixation point to the target was approximately 9 degrees. The resolution of the screen was 1024 x 1024 pixels and the sampling rate for the touch response was 75 samples/second (maximum temporal resolution = 13.3 ms).

The SDRT task is displayed in Figure 3. Each trial started with a 700 ms. presentation of a red central fixation dot against a black background. Then a white dot appeared in one of the positions specified in Figure 3 for 200 ms. Then the screen either went blank, except for the central fixation dot, and allowed for an immediate touch response or a two-digit number apeared in the middle of the screenfor 8 s. In the latter case, participants were required to count backward by threes starting with the number on the screen. Then the number disappeared, allowing for a delayed touch response. Subjects were instructed to make the response as accurately as possible by using the index finger of their dominant hand to point to the location where the dot appeared on the touch sensitive screen. After they made their response, the screen went blank. Then there was a 3 s inter-trial interval before the next trial began. Four or more practice trials (two with a delay and two without a delay) were administered and completion of the SOP was attempted only after it was clear that the task instructions were fully understood. Thirt-two trials were administered (16 with a delay, 16 without) so that every stimulus point

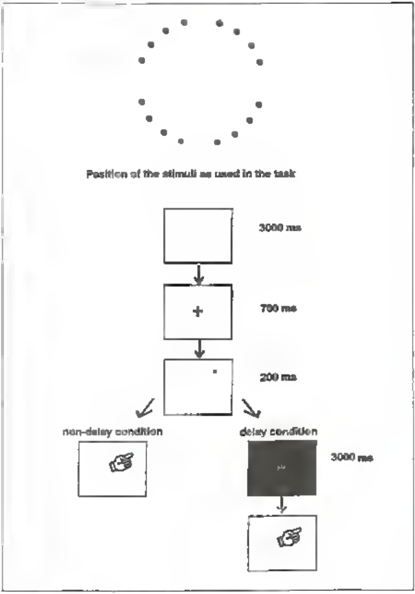
Position of the stimuli as used in the task
3000 ms
700 ms
200 ms
non-delay condition
delay condition
3000 ms

Figure 3. Spatial delayed response task.

was presented once in each condition. The sensory condition was always presented first, followed by the memory condition. Target presentation followed a pseudo-random order in that each location was only respresented once within each test, however the order of presetation was randomized for each participant. The computer record the x- and y coordinates of each response based on pixel coordinates. Response accuracy was calculated by measuring the distance of each response from the correct position of the dot.

Self ordered pointing task (SOP). An abbreviated version of Petrides and Milner's (1985) protocol, involving two SOP tasks, were administered to all participants. An example of a single trial of the most difficult block is provided in Figure 4. Each task consists of four sets of three trials. On the first (i.e., least difficult) block of the non-verbal SOP task, subjects view a series of six pages each displaying a 2 x 3 matrix of cells, each cell containing a black and white abstract design. For each page the subject is required to point to a design that he/she has not yet pointed to. Three trials of the same six designs are presented. The remaining three Blocks are similar, but each Block uses a different selection of designs, and the number of designs and pages increases to 8, 10, and 12 on the second, third, and fourth sets, respectively. The verbal SOP task is identical, with the exception that it uses abstract words instead of designs. A practice trial using numbers and letters was administered before the experimental tasks to ensure that the participants comprehended the instructions. The order of administration (i.e., abstract design SOP, the verbal SOP) remained constant for all participants to discourage the use of verbal strategies on the

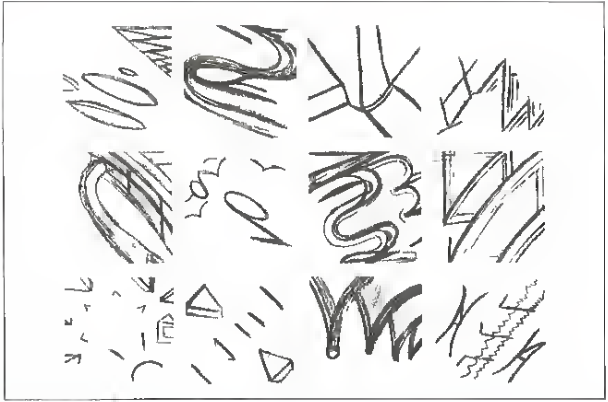

Figure 4. Self ordered point task (Petrides & Milner 1982)

abstract design task. Each SOP task was self paced with the exception that individuals are asked to respond more quickly if they are too slow or, conversely, they are asked to slow down if they respond too quickly. Petrides and Milner (1982) used this method because responses that are made too quickly may be a result of impulsivity and long response latencies may increase the long term memory demands of the task. When individuals responded to the same spatial location on more than three consecutive pages, they were told that they got to respond to the same location on every trial. Similarly, when they pointed to the words in alphabetical order, they were told that this strategy was not allowed. Response accuracy was recorded for each trial.

Control task: phonemic discrimination

This task, including the materials and design, were kindly supplied by Sheila Blumstein, who has used the task to investigate language comprehension deficits at the level of phoneme analysis (Blumstein, Baker, & Goodglass, 1975). An abbreviated version of Blumstein's (1975) phonemic discrimination task was administered to all participants. Participants were tested individually in a room with a 71dB sound pressure level (SPL, measured with a B&K Type 2209 sound level meter and a 1/3 octave filter set type 1616). Participants were seated facing a blank wall wearing a set of stereophonic earphones. Input into the headphones was independently adjusted on the audiometer to 40+ dB SPL. With a room noise level of 71 dB, this required a headphone output of at least 88 dB SPL with individual adjustment to the "just comfortable loudness level" (JCL). The JCL was determined by presenting auditory stimuli at gradually increasing loudness until participants reported some discomfort. At that point, the volume was turned down slightly until the individual reported no discomfort and good volume level.

Prior to every test session, participants received a training procedure to insure comprehension of the task. This procedure consisted of presentation of four pairs of stimuli, two of which were identical pairs (e.g. gib-gib) and two of which were contrasting (deb-beb). After each pair, participants responded by saying "yes" if both stimuli were perceived as identical or "no" if they were perceived as different.

Test stimuli consisted of 72 one-syllable non-word speech sounds. On half of the trials, the non-words were identical (e.g. dib-dib) and on the other half they were different (dib-gib). Each pair was presented twice, once with each member appearing in the first position. For each of these pairs there was a corresponding *control* pair where the first stimulus is repeated. The resulting 144 pairs were presented in pseudo-random order; no more than four identical or different pairs were presented sequentially. Prior to creating the task, each of the 72 individual nonsense words was recorded once by a male speaker. These recordings were used to create the series of speech sounds used in the task. Thus, for each occurrence of a particular item, the identical recorded segment was used. There was a two second delay between each member of a test pair, and approximately five seconds between each test item.

Magnetic Resonance Imaging

Scan protocol

Two scan sequences were performed in the Siemens Magnetom using a quadrature head coil. The first scan protocol consisted of a gradient echo volumetric acquisition "Turboflash" MP Rage sequence (TR = 10 ms, TE = 4 ms, FA = 10°, 1 acquisition, 25 cm field of view, matrix = 130 x 256, 6.03 min.). Images were reconstructed into a gapless series of 128 1.25-mm thick sections in the sagittal plane. The second protocol was a traditional axial scan of 5-mm T2 and spin density weighted images separated by 2.5 mm gaps (time = 8 min) obtained for examination of possible gross pathology. The images were transferred to the hard disk of a Sun SPARC station in the Neuroimaging Laboratory (NILab) by network. In the NILab each scan is assigned a blind number from a randomly generated list. Programs written in PV Wave (a programming language designed for handling large arrays from Visual Numerics, Inc. Boulder CO) stripped the headers, reduce the data from 16 to 8 bits per pixel, and placed the images into a single file labeled with the blind number. This file contained all sagittal images containing brain. Films were sent to a neuroradiologist to examine for clinically significant findings.

Standardization and reformatting

In order to insure that comparable regions were examined in each brain, the Talairach proportional grid method (Talairach & Tournoux, 1988) was used. The Talairach system standardizes positions by relating them to standard planes in one brain that measured 69 mm wide in the left hemisphere and 67 mm wide in the right hemisphere. The horizontal plan intersects the anterior and posterior commissures. Coordinates in the brain are referred to in those dimensions. For example, the hippocampus is found between Talairach coordinates (Tal) 17.5 and 35. The PV-Wave programs convert the section numbers to this coordinate system in the sagittal plane but use real mm for calculating distances. After a degree of head tip in each of the orthogonal planes is determined, the scans are reformatted into a final set of sagittal and coronal scans in the Talairach planes. These series have isotropic voxels measuring 1 mm in each dimension.

Definition of brain regions

Area 46. An estimate of area 46 (area 46) was measured volumetrically. In defining area 46, we relied primarily on findings from cytoarchitectonic studies (Rajkowska & Goldman Rakic, 1994, Petrides & Pandya, 1994). Rajkowska and Goldman Rakic looked at six postmortem brains and mapped out the cyoarchitecture of the prefrontal cortices. They then defined subdivisions of the prefrontal cortex (i.e. areas 46 and 9) in terms of morphological landmarks and Talairach space. Although the bulk of area 46 lies primarily along the middle frontal gyrus (MFG), for some individuals its borders may extend into the superior or inferior frontal sulci and gyri (Goldman Rakic, 1994, Petrides & Pandya, 1994). A large portion of area 46 occupied a region of the middle frontal gyrus in all six brains. This region was between Talairach coordinates 29 and 51 in the AP plane.

The MFG is bounded by the superior (SFS) and inferior frontal sulci (IFS DeArmond, Fusco, & Dewey, 1989; Roberts, Hanaway, & Morest, 1987). However, these boundaries are not always unambiguous. Volumetric measures were made in the coronal plane, which makes it particularly difficult to follow these sulci because the entire length of the sulcus is not visible on any one slice. There are numerous sulci in the prefrontal region which intersect with or look similar to IFS and SFS. In a sample of twenty five postmortem brains, the left IFS was continuous in only 40% of the population and intersected with other sulci in 32% of cases (Ono, Kubik, & Abernathy, 1990). The middle frontal sulcus (MFS), also referred to as the intermediate frontal sulcus, runs horizontally through the MFG in more than 80% of individuals (Ono et al., 1990) and is sometimes difficult to distinguish from the SFS on coronal section. Observation in our laboratory suggest that some individuals may even have two MFSs. On coronal section, the SFS may also be confused with the medial frontal sulcus (MdFS), which Ono et al (1990) describe as being medial to the SFS. Because of this variability, we have developed explicit rules for measuring the area 46, region of the MFG reliably. A list of these rules are provided in Appendix B. The boundaries of MFG in its most anterior portion are not clear in coronal MRI sections. Therefore, only the images between Talairach coordinates 32 and 45 in the AP plane were measured as an estimate of area 46.

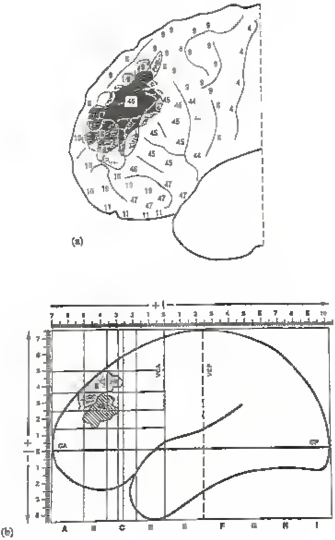
(a)
45
46
47
9
10
11
(b)
CA
CP
VCA
VCP
A
B
C
D
E
F
G
H
I

Figure 5. Rajkowska & Goldman-Rakic (1995) mapping of prefrontal cortex based on (a) cytoarchitecture and (b) Talairach space

Results from a pilot study using these criteria in 10 schizophrenics and 10 normal control brains yielded Pearson r interrater reliabilities of .83 and greater for the left and right MFGs. Reliability was also assessed by examining the degree to which the absolute value of the rater's measures were the same as opposed to correlated. This was done by taking the larger of the two measures, subtracting the smaller of the measures, dividing by the larger value, multiplying by 100, and subtracting the resulting value from 100, i.e., 100 - 100 (large value-small value / large value). The percentage of overlap represents the degree to which the two measures are the same. For example, for the measures 6 cc and 7 cc, the percent overlap is 85.7%. Percent overlap for two raters was 88 percent.

Control brain region, planum temporale. In individuals with one clearly defined Heschl's gyrus, the anterior border of the planum is defined as the depth of the sulcus that is the posterior border of Heschl's gyrus (Heschl's sulcus). Thus, a second Heschl's gyrus that sometimes appears somewhat lateral to the insula was included in the planum measurements. The posterior boundary was defined as the origin of the posterior ascending ramus or the termination of the Sylvian fissure. The surface of the planum was measured sequentially on every section between Talairach units L47 and L56. Areas measured in this way predict language laterality (Foundas, Leonard, Gilmore, Fennell, & Heilman, 1994), handedness (Foundas, Leonard, & Heilman, 1995), and phonemic awareness (Leonard, Lombardino, Mercado, Browd, & Roper, 1996).

Volumetric measures

The MFG was traced manually with a mouse-operated cursor, on the image displayed on the Sun™ work station monitor. For each brain approximately twelve images in each hemisphere were traced in the coronal plane. The surface area of each image was calculated by a program written in PV Wave. The surface area of each section was multiplied by its thickness (i.e. 1 mm) and the volumes of the twelve images were summed to get the total volume the portion of area 46_d, from Tal 39 to 55 in each of the two hemispheres.

The planum was measured in sagitial section. The length of the planum was traced on each slice and a total surface area was calculated in PV Wave by multiplying the length by the width of the section (i.e. 1 mm) and adding successive sections together.

Measurements of hemispheric and total brain volumes were also be made in order to control for the effects of possible generalized brain atrophy. The exterior borders of the left and right hemispheres were traced in sagittal plane. Every fourth slice was measured and volume was calculated by multiplying the area of each slice by the distance between sections (4 mm) and summing the values to yeild left, right, and total hemisphere volumes.

RESULTS

The main focus of this study was to test the hypothesis that negative symptoms are associated with dorsolateral prefrontal pathology detectable through measures of both regional brain morphology and cognitive functioning. Before addressing the questions of interest, several sets of exploratory analyses were performed. First, relationships between demographic variables and dependent measures (i.e. symptom ratings, cognitive measures, volumetric MRI measures) were explored with Pearson *r* correlations in order to identify other factors contributing to the variance of the dependent measures. Second, the relationships among the different cognitive measures were explored in order to determine the specificity of the individual cognitive tests. Third, relationships between volumetric MRI measures and cognitive performance were examined in order to test the assumption that performance on specific cognitive tests is related to specific regional brain volumes.

Following the exploratory analyses, three broad questions are addressed: (a) Is working memory performance related to negative symptoms? (b) Is the size of area 46_c related to negative symptoms? (c) Are there group differences between schizophrenic patients and controls that may reflect an underlying process that is common to all forms of schizophrenia? Each of these questions, respective hypotheses, and results of statistical analyses are discussed below. Although questions (a) and (b) were of primary interest in this study, question (c) is addressed first because group differences appeared to influence the correlational analyses in this study.

Correlations Between Demographic Variables and Dependent Measures

Pearson *r* correlations were conducted to examine the relationships between dependent measures (i.e., symptoms, cognitive performance, and MRI measures) and demographic variables (i.e., age, parental SES, quantitative handedness, height, weight, length of illness, frequency of hospitalizations).

Correlations Between Demographic Variables and Symptom Clusters

Mean symptom cluster scores are provided in Table 2 and demographic data provided in Table 1. Demographic variables in these analyses included age, parental SES, quantitative handedness, length of illness, frequency of hospitalizations. Symptom clusters included negative, positive, disorganized, and general psychopathology symptoms. A total of 44 correlations were performed. At least two correlations were expected to be significant based on chance alone. None of the symptom cluster scores were significantly associated any of the demographic variables across groups or within the schizophrenic group alone.

Correlations Between Demographic Variables and Cognitive Performance

Descriptive statistics for cognitive performance are provided in Table 3. Demographic variables in these analyses included age, parental SES, quantitative handedness, length of illness, and frequency of hospitalizations. Cognitive variables included VIQ, PIQ, FSIQ, memory SDRT error distance, memory SDRT response time, sensory SDRT error distance, sensory SDRT response time, verbal SOP errors and nonverbal SOP errors. A total of 99 correlations were performed. At a $p < .05$ level, at least 5 correlations were expected to be significant by chance. Only 2 correlations were significant. Higher percent errors on the verbal SOP task was associated with older age across groups ($r = .41$, $p < .007$). When the groups were examined individually, this relationship was seen in the control group ($r = .64$, $p < .002$), but not the schizophrenic group ($r = .19$, $p < .39$).

Correlations Between Demographic Variables and Volumetric MRI Measures

Descriptive statistics for MRI variables are provided in Table 4. Volumetric MRI measures included right, left, and total area 46, volumes; right, left, and total hemisphere volumes; right and left planum areas, and planar asymmetry. Demographic variables included age, quantitative handedness, parental SES, height, weight, length of illness, and frequency of hospitalizations. A total of 153 correlations were performed. At least 7 significant correlations were expected to occur by chance at the $p < .05$ level.

Table 3

Cognitive Performance of Patients and Controls

	Groups			
	Controls n=23		Schizophrenics (n=23)	
Variable	*M*	*SD*	*M*	*SD*
Intellectual				
VIQ	117.65	16.44	98.04	11.36
PIQ	116.17	11.91	91.13	10.29
FSIQ	115.91	11.55	94.74	9.75
Memory SDRT				
error distance	3.56	1.33	5.52	3.33
response times	1366.26	257.62	2167.65	1271.03
Sensory SDRT				
error distance	2.16	1.47	2.16	1.06
response times	1016.70	265.52	1172.65	467.12
Verbal SOP errors				
Block 1	5.56	5.63	11.11	6.54
Block 2	8.51	7.04	17.57	6.46
Block 3	9.42	6.61	15.94	6.19
Block 4	9.36	7.56	17.75	7.14
Nonverbal SOP errors				
Block 1	6.76	6.03	14.73	8.14
Block 2	11.77	6.20	16.75	10.15
Block 3	16.26	6.86	16.55	9.26
Block 4	9.78	5.61	19.93	5.61
Phonemic				
Discrimination errors	7.57	4.42	14.48	1.56

Note. SDRT error distances reflect *relative* distance (i.e. number of target radii) from the touch response to the target position. Verbal and nonverbal SOP errors are percent errors.

The number of significant correlations did not exceed chance levels. Only 7 of the 153 correlations were significant. Across group correlations revealed a significant relationship between more extreme right handedness scores and larger right area 46, volumes ($r = .37$, $p < .02$) and lower parental SES was associated with larger left plana ($r = .31$, $p < .05$). Within the schizophrenic group there were significant relationships between more extreme right handedness scores and larger total ($r = .45$, $p < .03$) and right area 46, volumes ($r = .59$, $p < .003$) and between lower parental SES and larger total planum temporale areas ($r = .55$, $p < .007$). Similarly, controls demonstrated only two significant correlations: lower parental SES was associated with larger left ($r = -.45$, $p < .03$) and total ($r = -.48$, $p < .04$) area 46, volumes.

Summary of Correlations Between Demographic Variables and Dependent Measures

Demographic variables generally were not associated with symptom measures, cognitive performance, and volumetric MRI measures. While some significant correlations existed, it was expected that at least that many correlations would have occurred by chance given the number of correlations conducted.

Correlations Between Cognitive Measures

Pearson r correlations were conducted to explore relationships between all cognitive variables including IQ, SDRT, SOP, and PD performance. Three sets of analyses were conducted. First, correlations were conducted across groups. Then,

Table 4

Mean Size of Brain Structures

	Groups			
	Controls n=23		Schizophrenics (n=23)	
Variable	*M*	*SD*	*M*	*SD*
Area 46				
Right	90	17	92	.21
Left	84	19	84	18
Total	87	14	.88	17
Planum temporale				
Right	2.62	0.95	2.17	0.95
Left	3.88	0.90	3.72	1.05
Asymmetry	.27	.32	38	28
Hemisphere				
Right	653.87	60.29	638.78	65.65
Left	663.97	81.54	648.77	65.62
Total	1317	134.46	1278	127.46

Note. Area 46_a measures are expressed as the percentage volume occupied in its respective hemisphere (i.e. right area 46_a volume/ right hemisphere volume * 100). Planum temporale measures are expressed in mm^2. Hemisphere measures are expressed in cm^3

correlations were conducted within the individual groups in order to determine whether relationships among cognitive variables differ for the two group. It was expected that performance on the SOP and memory SDRT tasks would be associated with each other because they are both working memory tasks. In contrast, we did not expect performance on these tasks to be associated with performance on the PD task.

Across Group Correlations

Pearson r values describing relationships between cognitive variables are provided in Table 5. Across groups, higher intellectual functions were related to smaller error distances ($r = -.51$, $p < .0001$) and faster response times ($r = -.43$, $p < .003$) on the memory SDRT task, fewer errors on the SOP task ($r = -.78$, $p < .0001$), and fewer errors on the PD task ($r = -.57$, $p < .0001$). Error distance and response times on the sensory SDRT task were not significantly related to IQ. Higher percent errors on the SOP task were associated with higher error rates on the PD task ($r = .56$, $p < .0001$), and larger error distances ($r = .63$, $p < .0001$) and longer response times ($r = .58$, $p < .0001$) on the memory SDRT task. Larger error distances and longer response times on the memory SDRT task also were associated with higher error rates on the PD task ($r = .49$, $p < .001$; $r = .52$, $p < .0001$, respectively). Performance on the sensory SDRT task was not associated with performance on the SOP or PD tasks.

Schizophrenic Group Correlations

Correlations conducted within the schizophrenic group were largely consistent with across group analyses. Higher intellectual functions were associated with smaller error distances ($r = -.56$, $p < .006$) and faster response times ($r = -.44$, $p < .04$) on the memory SDRT, decreased errors on the SOP task ($r = -.71$, $p < .0001$), and decreased errors on the PD task ($r = -.62$, $p < .002$). Increased errors on the SOP task were associated with increased error distance on the memory SDRT task ($r = .71$, $p < .0001$) and increased errors PD tasks ($r = .53$, $p < .01$). Larger error distances on the memory SDRT task were associated with increased error rates on PD task ($r = .46$, $p < .03$). Longer response times on the memory SDRT task also were associated with increased error rates on PD task ($r = .46$, $p < .03$). Unlike the across group correlations, larger error distances on the sensory SDRT task were associated with lower FSIQ scores ($r = -.60$, $p < .002$), increased errors on the SOP task ($r = .60$, $p < .002$), and increased errors on the PD task ($r = .45$, $p < .03$). Response times on the sensory SDRT task were not associated with any of the other cognitive measures.

Control Group Correlations

Among control subjects higher FSIQ scores were associated with lower error rates on the SOP task ($r = -.52$, $p < .01$). There were no association between the other cognitive variables. Controls demonstrated a wide range of variability on the SOP task. In contrast, their range of performance on the SDRT and PD tasks was more restricted, which may account for the lack of associations between these cognitive measures.

Table 5

[illegible]

	FSIQ		Memory SDRT error distance		Memory SDRT–RT		Sensory SDRT error distance		Sensory SDRT RT		SOP total errors		PD errors	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
							Combined Groups							
FSIQ			51	000*	43	003*	12	42	12	42	78	000*	57	000*
Memory SDRT error distance			–	–	77	000*	57	000*	28	06	63	000*	49	001*
Memory SDRT RT					–	–	31	03**	44	002	58	000*	52	000*
Sensory SDRT error distance								–	07	63	20	18	1[illegible]	01*
Sensory SDRT RT											30	04**	37	[illegible]
SOP total errors											–	–	5[illegible]	[illegible]
PD errors														

Note. * Significant at p < 01 **Significant at p < 05

Table 5 continued

	FSIQ		Memory SDRT error distance		Memory SDRT RT		Sensory SDRT error distance		Sensory SDRT RT		SOI total errors		PD errors	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
							Schizophrenic Patients							
FSIQ	—	—	-36	006*	44	04**	.60	002*	26	23	71	001*	12	[illegible]
Memory SDRT error distance			—	—	81	000*	76	000*	24	26	71	000*	46	03**
Memory SDRT RT					—	—	.63	001*	40	06	.57	004*	47	03**
Sensory SDRT error distance							—	—	20	36	.60	002*	45	03**
Sensory SDRT RT										—	35	10	32	13
SOI total errors											—	—	53	01*
PD errors													—	—

Note. * Significant at $p < .01$ ** Significant at $p < .05$

Table 5 continued

	FSIQ		Memory SDRT error distance		Memory SDRT RT		Sensory SDRT error distance		Sensory SDRT RT		SOP total errors		PD errors	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
							Controls							
FSIQ		—	15	49	16	48	06	77	23	30	53	[illegible]	[illegible]	[illegible]
Memory SDRT error distance					06	78	69	000*	11	61	[illegible]	[illegible]	13	88
Memory SDRT RT							69	000*	59	003*	11	[illegible]	14	.52
Sensory SDRT error distance									05	84	09	69	22	31
Sensory SDRT RT									—	—	16	45	31	[illegible]
SOP total errors											—		[illegible]	[illegible]
PD errors														—

Note. * Significant at $p < .01$ ** Significant at $p < .05$

Summary of Correlations Between Cognitive Measures.

These results suggest that among schizophrenics, there is considerable shared variance between all of the cognitive measures, with the exception of response time on the sensory SDRT task. Controls also demonstrated a relationship between SOP performance and FSIQ but did not demonstrate relationships among the other cognitive variables. The finding that schizophrenics show strong associations among all cognitive measures and that controls do not may be a result of greater variability in performance of the schizophrenics compared to the controls. Alternatively this difference may be a result in differences in functional brain circuitry.

Correlations between Volumetric MRI and Cognitive Measures

Pearson *r* correlations were conducted to explore relationships between cognitive variables and brain measures. Two sets of analyses were conducted. First, correlations between MRI and cognitive measures were conducted across groups. Second, within group correlations were conducted to explore the how MRI measures are differentially related to cognitive performance of schizophrenics and controls. Based on previous animal lesion and human functional imaging research, it was expected that working memory performance on the SOP and memory SDRT tasks would be associated with area 46, volumes; smaller area 46, volumes would be related to greater error rates and longer response times. It was expected that the size of area 46, would not be associated with performance on the phonemic discrimination or IQ tasks. Since the planum temporale consists of auditory association cortex, smaller left plana were expected to be associated with increased errors on the phonemic discrimination task, but not performance on working memory or IQ tasks. Finally, hemispheric volumes were expected to be correlated with IQ; larger left, right and/or total hemispheric volumes would be related to higher FSIQ scores.

Area 46_r and Cognitive Performance

Pearson *r* values are provided in Table 6. Contrary to our hypothesis, area 46_r measures were not related to performance on the working memory tasks across or within groups. In fact, area 46_r measures were not associated with performance on any of the cognitive tasks employed.

Planum Temporale and Cognitive Performance

Pearson *r* correlations are provided in Table 7. Contrary to our hypothesis, planum measures were not associated with phonemic discrimination across or within groups. Planum measures also were not associated with IQ or working memory.

Hemisphere Volumes and Cognitive Performance

Pearson *r* correlations are provided in Table 8. Contrary to our predictions, hemispheric volumes were not associated with IQ performance across or within groups. Schizophrenic patients with longer response times on the memory SDRT task had larger total brain volumes ($r = .44$, $p < .04$). Control did not show this association.

Table 6

Pearson r Correlations between Area 46, and Cognitive Measures

	Area 46 Measure					
	Left		Right		Total	
Cognitive Test	*r*	*p*	*r*	*p*	*r*	*p*
			Combined Groups			
WAIS-R						
VIQ	-.08	.83	.06	72	.01	93
PIQ	-.05	78	16	30	.07	66
FSIQ	-.05	74	11	30	.03	.84
Memory Spatial						
Delayed Response						
Error Distance	.00	1.00	.01	93	03	.87
Response Time	-.04	79	10	31	03	.83
Sensory Spatial						
Delayed Response						
Error Distance	-.02	.91	.03	86	04	79
Response Time	001	.99	15	33	-.07	.64
Self Ordered						
Pointing Errors						
Verbal	.007	97	19	.22	-.12	.45
Nonverbal	.04	78	14	.36	-.03	73
Total	.02	89	17	.27	14	.36
Phonemic Discrimination Errors	01	93	.08	.60	.04	80

Table 6 continued

	Area 46, Measure					
	Left		Right		[illegible]	
Cognitive Test	*r*	*p*	*r*	*p*	[illegible]	[illegible]
			Schizophrenic Patients			
WAIS-R						
VIQ	09	.67	13	.55	13	55
PIQ	.07	76	.29	18	.22	32
FSIQ	.08	71	.25	.26	.20	36
Memory Spatial						
Delayed Response						
Error Distance	-.06	78	.02	.92	.01	96
Response Time	-.07	74	11	60	08	71
Sensory Spatial						
Delayed Response						
Error Distance	18	.42	-.04	.87	.08	72
Response Time	.20	.35	-.11	.63	-.09	66
Self Ordered						
Pointing Errors						
Verbal	10	.38	.39	06	.36	10
Nonverbal	11	.61	.27	.22	.23	.28
Total	17	44	-.34	11	.28	19
Phonemic						
Discrimination Errors	11	.62	05	.82	-.09	68

Table 6 continued

	Area 46, Measure					
	Left		Right		Total	
Cognitive Test	*r*	*p*	*r*	*p*	*r*	*p*
			Controls			
WAIS-R						
VIQ	−.08	.85	.06	.72	.01	.93
PIQ	−.05	.78	.16	.30	.07	.66
FSIQ	−.05	.74	.11	.50	.03	.84
Memory Spatial Delayed Response						
Error Distance	.18	.40	−.07	.76	.24	.27
Response Time	.12	.58	.11	.63	.11	.60
Sensory Spatial Delayed Response						
Error Distance	-.18	.41	.22	.31	.18	.41
Response Time	.30	.16	.14	.53	.11	.60
Self Ordered Pointing Errors						
Verbal	.17	.49	.006	.98	.11	.65
Nonverbal	.23	.33	.03	.88	.16	.51
Total	.17	.43	−.18	.42	−.03	.89
Phonemic Discrimination Errors	.09	.72	.19	.43	.24	.31

Table 7

Pearson r Correlations between Planum Temporale and Cognitive Measures

	Planum Temporale Measure					
	Left		Right		Asymmetry	
Cognitive Test	*r*	*p*	*r*	*p*	*r*	*p*
			Combined Groups			
WAIS-R						
VIQ	11	.50	12	.44	-.14	36
PIQ	.06	68	-.02	89	.02	92
FSIQ	-.11	.50	07	.68	09	.57
Memory Spatial						
Delayed Response						
Error Distance	008	96	-.14	38	08	62
Response Time	13	42	15	35	01	96
Sensory Spatial						
Delayed Response						
Error Distance	07	66	.001	99	02	90
Response Time	.32	04*	.21	17	-.02	89
Self Ordered						
Pointing Errors						
Verbal	-.03	.84	.01	.93	-.09	57
Nonverbal	-.20	.20	13	.42	-.07	.65
Total	-.14	38	.08	61	09	.58
Phonemic						
Discrimination Errors	-.06	.69	.08	.60	02	90

Note. * Significant at $p < .05$

Table 7 continued

	Planum Temporale Measures					
	Left		Right		Asymmetry	
Cognitive Test		p	r	p	r	p
			Schizophrenic Patients			
WAIS-R						
VIQ	02	93	04	98	05	83
PIQ	.01	96	.22	32	30	16
FSIQ	.003	99	07	74	17	.43
Memory Spatial						
Delayed Response						
Error Distance	10	.05	-.16	48	01	95
Response Time	-.11	.62	-.09	71	.05	90
Sensory Spatial						
Delayed Response						
Error Distance	-.02	91	05	84	.03	90
Response Time	.43	.04*	35	11	.007	98
Self Ordered						
Pointing Errors						
Verbal	-.04	.84	.08	71	.21	.34
Nonverbal	-.31	16	03	89	.31	15
Total	-.19	.37	.07	74	.29	10
Phonemic Discrimination Errors	05	83	-.05	81	-.003	98

Note. * Significant at $p < .05$

Table 7 continued

	Planum Temporale Measure					
	Left		Right		Asymmetry	
Cognitive Test	*r*	*p*	*r*	*p*	*r*	*p*
			Controls			
WAIS-R						
VIQ	.43	.06	-.16	.50	-.13	.59
PIQ	.29	.24	-.27	.24	.08	.73
FSIQ	.41	.07	-.22	.35	.05	.83
Memory Spatial Delayed Response						
Error Distance	.36	.12	.19	.39	.008	.97
Response Time	.31	.19	.11	.64	.16	.50
Sensory Spatial Delayed Response						
Error Distance	.17	.48	.04	.87	.06	.82
Response Time	.09	.68	.09	.69	-.19	.43
Self Ordered Pointing Errors						
Verbal	.05	.82	.32	.17	.36	.12
Nonverbal	.04	.88	.04	.85	.04	.85
Total	-.04	.88	.11	.62	.22	.35
Phonemic Discrimination Errors	-.09	.72	.19	.43	-.24	.31

Table 8

Pearson *r* Correlations between Hemisphere and Cognitive Measures

	Hemisphere Measure					
	Left		Right		Total	
Cognitive Test	*r*	*p*	*r*	*p*	*r*	*p*
			Combined Groups			
WAIS-R						
VIQ	02	.92	01	93	.02	.92
PIQ	.05	74	-.13	.43	-.09	.58
FSIQ	-.03	.84	.07	.65	.05	74
Memory Spatial						
Delayed Response						
Error Distance	03	.84	08	.63	.05	73
Response Time	22	16	.25	11	.24	12
Sensory Spatial						
Delayed Response						
Error Distance	15	.34	16	32	16	.31
Response Time	01	.94	.07	85	.04	80
Self Ordered						
Pointing Errors						
Verbal	.007	97	002	99	009	97
Nonverbal	21	18	19	39	15	.24
Total	-13	.41	09	55	12	.46
Phonemic Discrimination Errors	06	71	02	89	.04	78

Table 8 continued

	Hemisphere Measure					
	Left		Right		Total	
Cognitive Test	*r*	*p*	*r*	*p*		*p*
			Schizophrenic Patients			
WAIS-R						
VIQ	09	.68	05	83	-.07	75
PIQ	-32	14	25	.24	.29	18
FSIQ	24	.28	18	40	-.21	.33
Memory Spatial						
Delayed Response						
Error Distance	10	.64	11	62	11	.62
Response Time	43	04*	43	04*	.44	04*
Sensory Spatial						
Delayed Response						
Error Distance	08	71	.09	69	09	70
Response Time	14	.53	18	.41	16	.46
Self Ordered						
Pointing Errors						
Verbal	05	80	001	1 00	03	90
Nonverbal	02	92	02	92	.001	1 00
Total	04	.85	02	04	.01	95
Phonemic Discrimination Errors	12	.57	08	73	10	.64

Note. * Significant at $p < .05$

Table 8 continued

	Hemisphere Measure					
	Left		Right		Total	
Cognitive Test	r	p	r	p	r	p
			Controls			
WAIS-R						
VIQ	.28	.24	-.27	24	-.29	[illegible]
PIQ	.23	.32	-.48	08	-.32	[illegible]
FSIQ	.31	19	.39	09	-.36	[illegible]
Memory Spatial Delayed Response						
Error Distance	.22	.32	.34	11	.28	19
Response Time	36	.09	.23	28	.33	[illegible]
Sensory Spatial Delayed Response						
Error Distance	07	75	.05	82	06	77
Response Time	02	92	.07	74	05	84
Self Ordered Pointing Errors						
Verbal	37	11	.39	09	40	08
Nonverbal	-.31	18	11	65	-.24	.31
Total	-.11	.62	03	88	.09	71
Phonemic Discrimination Errors	-.18	.46	-.03	90	-.12	.61

Summary of Correlations between Volumetric MRI and Cognitive Measures

In summary, results of these analyses failed to support our hypotheses regarding relationships between cognitive and brain measures. Area 46_c volumes were not associated with working memory performance, plana measures were not associated with phonemic discrimination, and hemisphere volumes were not associated with IQ. The lack of correlations between brain variables and cognitive functions could be due to several factors. The validity of both cognitive and MRI measures and the hypothesis that size of brain structures is related to cognitive functioning need to be explored. These issues are discussed further in the Discussion section below.

Group Differences

Are there group differences between schizophrenic patients and controls that may reflect an underlying process that is common to all forms of schizophrenia? This question was exploratory in nature. We did not make specific hypotheses regarding group differences in cognitive and brain measures because it already is known that schizophrenic patients demonstrate significant variability with regard to both cognitive performance and brain morphology. In general, it was expected that schizophrenic patients would have higher symptom ratings than controls. The average cognitive performance of the schizophrenic group was expected to be poorer than controls, but it was also expected that many patients would fall within normal limits. Similarly, it was expected that schizophrenic patients may have smaller mean total and regional brain volumes, but that some would be within normal limits.

Symptom Ratings

Mean PANSS individual symptom and cluster scores for each group are presented in Table 2. As expected, the schizophrenic group demonstrated more severe pathology than the control group on each of the thirty-two symptom scales. Each cluster score was transformed into a percentage of possible points score in order to make comparisons across clusters. For example, the maximum score attainable for the positive symptom cluster is forty-two (six symptoms with a maximum rating of seven); the percentage score for a summed score of twenty-one would be 50%. Results of a 2 (Group) x 3 (Cluster) ANOVA with repeated measures on the cluster factor revealed that, as expected, the groups differed with regard to overall severity of symptoms: schizophrenic patients displayed higher percentage scores across all symptom clusters, $F(1, 40) = 126.41$, $p < .0001$. The cluster effect and the Group x Cluster interaction were not significant, suggesting that within each group, participants received comparable severity ratings across symptom clusters.

Cognitive Performance

Two sets of analyses were performed for each cognitive measure. In light of the findings of significant shared variance between working memory and FSIQ, analyses examining group differences in neuropsychological test performance were approached in two ways. First, ANOVAs were conducted examining group differences in test performance. Second, FSIQ was entered into the analyses as a covariate to examine differences between groups equated for IQ. There are advantages and problems associated with these approaches. In the first case, group differences on specific neuropsychological tasks may be a result of global decline in cognitive functioning which will not be revealed by an ANOVA that does not account for group differences in FSIQ. However, FSIQ may be highly associated with performance on working memory tasks because they tap common cognitive processes and removing that variance from the analysis may statistically weaken potentially significant differences between groups. Results from both ANOVAs and ANCOVAs are presented and discussed below.

Intellectual functions

Mean IQ scores for each group are provided in Table 4. A one-way ANOVA revealed that the schizophrenic patients had lower overall FSIQ scores than the controls (controls, M = 115.91, SD = 11.55; schizophrenics, M = 94.74, SD = 9.75), $F(1, 44) = 45.10$, $p < .001$. A subsequent 2 (Group) x 2 (Domain: VIQ, PIQ) ANOVA with repeated measures for the Domain factor revealed that the control group obtained higher scores, overall, than the schizophrenic group, $F(1, 44) = 46.85$, $p < .001$. Both groups obtained higher VIQ than PIQ scores (VIQ, M = 107.85; PIQ, M = 100.65), $F(1, 44) = 19.92$, $p < .001$. There was no significant Group x Domain interaction. Similar results were obtained when age was controlled as a covariate in the analysis.

Spatial delayed response task

Error distance. Mean error distance per condition per group are provided in Table 4. Data are displayed graphically in Figure 4. A 2 (Group) x 2 (Condition) ANOVA with repeated measures for the condition factor revealed a main effect of condition, $F(1, 44) = 63.43$, $p < .001$, and a Group x Condition interaction, $F(1, 44) = 11.27$, $p < .003$. The nature of this interaction was explored with ANOVAs conducted separately within each group and condition. Within the schizophrenic group, performance was worse in the memory compared to the sensory condition (sensory, $M = 2.17$, memory, $M = 5.53$), $F(1, 22)$, $p < .0001$. Similarly, controls performed better in the sensory compared to the memory condition (sensory, $M = 2.19$, memory, $M = 3.56$), $F(1, 22) = 34.35$, $p < .0001$. While the two groups performed comparably in the sensory condition, the schizophrenic group performed more poorly than controls in the memory condition (schizophrenics, $M = 5.52$, $SD = 3.33$; controls, $M = 3.56$, $SD = 1.33$), $F(1, 44) = 6.88$, $p < .01$. These results suggest that while both schizophrenics and controls performed better in the sensory compared to the memory condition, the schizophrenic patients performed disproportionately worse than controls in the memory condition.

When FSIQ was controlled in a 2 (Group) x 2 (Condition) ANCOVA with repeated measures for the condition factor, the group effect was no longer significant (adjusted means: controls, $M = 3.47$; schizophrenics, $M = 3.25$); however, the main effect of condition, $F(1, 42) = 60.55$, $p < .0001$, and the Group x Condition interaction, $F(1,42) = 10.75$, $p = .002$, remained significant.

Response times. Mean response times for each group are provided in Table 4. Data are depicted graphically in Figure 5. A 2 (Group) x 2 (Condition) ANOVA, with repeated measures for the condition factor, revealed significant effects of group, $F(1, 44)$

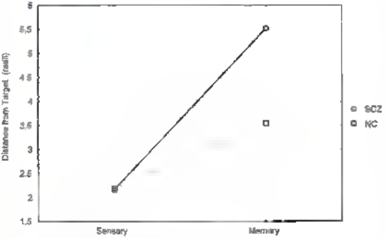

Figure 6. Mean SDRT error distance.
Error distance was measured as the distance of the touch response, in terms of the number of target radii, away from the center of the target.

= 7.29, $p < .009$), condition, $F(1, 44) = 27.50$, $p < .0001$, and a Group x Condition interaction, $F(1, 44) = 5.09$, $p < .03$. The nature of the interaction was explored with ANOVAs conducted separately within each group and condition. Both the schizophrenic and control groups responded faster in the sensory compared to the memory condition, controls, $F(1, 22) = 57.19$, $p < .0001$, schizophrenics, $F(1, 22) = 14.63$, $p < .001$. Within the sensory condition, there was no simple effect of group. In contrast, within the memory condition there was a significant group effect, $F(1, 44) = 7.05$, $p < .01$; schizophrenic patients were slower to respond than controls (schizophrenics, $M = 2108$ ms, $SD = 1272$ ms; controls, $M = 1389$ ms, $SD = 257$ ms).

When mean FSIQ was entered into the analyses as a covariate the group effect was no longer significant (adjusted means: schizophrenics, $M = 1517$ ms, controls, $M = 1326$ ms); however, the main effect of condition, $F(1, 43) = 26.88, p < .0001$, and the Group x Condition interaction, $F(1, 43) = 4.97, p < .03$, remained significant. The interaction was explored with follow-up ANCOVAs performed separately within group and condition. Both the schizophrenic and control groups responded faster in the sensory compared to the memory condition, controls: $F(1, 21) = 54.59, p < .0001$; schizophrenics: $F(1, 22) = 13.97, p < .001$. Within each condition, there was no main effect of group.

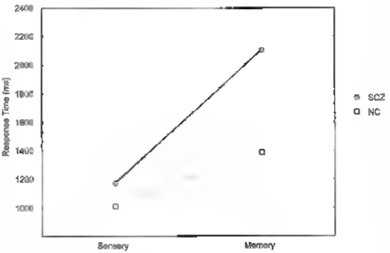

Figure 7. SDRT mean response times.
Response times were measured in milliseconds (ms).

Self-ordered pointing task

Mean percent errors for the verbal and nonverbal SOP task are provided in Table 2 and data are depicted graphically in Figure 8. A 2 (Group) x 2 (Condition: verbal, nonverbal) x 4 (Block) ANOVA with repeated measures for condition and block was conducted, adjusting means for multiple repeated measures with the Huynh-Feldt epsilon correction. Results of this analysis revealed that, overall, the schizophrenia group performed more poorly than controls (schizophrenics, M = 16.92%, controls, M = 8.92%), $F(1, 44) = 26.85$, $p < .0001$. Both groups made more errors in the nonverbal compared to the verbal condition (nonverbal, 13.95%, verbal, 11.90%), $F(1, 44) = 7.54$, $p < .008$. There also was a significant Block effect, $F(3, 132) = 19.58$, E = 1.00, $p < .0001$. There were no significant interactions.

Follow-up comparisons examining the nature of the Block effect indicated that participants performed better on Block 1 compared to each of the three other Blocks (Block 1 vs Block 2, $F(1, 44) = 44.58$, $p < .001$; Block 1 vs Block 3, $F(1, 44) = 24.44$, $p < .001$; Block 1 vs Block 4, $F(1, 44) = 40.65$, $p < .001$). Relative error rates were consistent across Blocks 2, 3, and 4.

When groups were equated for FSIQ in an ANCOVA with repeated measures for the condition and block factors, there was no longer a significant group effect (adjusted means: controls, M = 12.02, schizophrenics, M = 13.83). The condition and block effects remained significant, $F(1, 43) = 7.37$, $p < .009$; $F(3, 132) = 19.58$, E = 1.00, $p < .0001$, respectively, and there were no significant interactions.

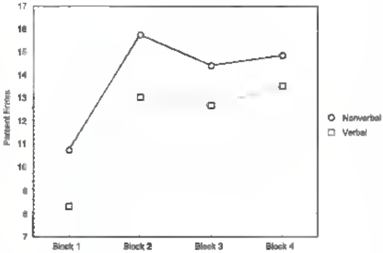

Figure 8. Mean verbal and nonverbal SOP percent errors per block.

Phonemic discrimination task

Mean errors for each group are reported in Table 2. A one-way ANOVA revealed a significant main effect of group, *F*(1, 44) = 71.67, *p* < .008. The schizophrenic group made more total errors than the control group (schizophrenics, *M* = 14.48, *SD* = 11.22; controls, *M* = 7.57, *SD* = 4.42). This effect failed to reach significance when FSIQ was entered into the analysis as a covariate (adjusted mean errors, schizophrenics, *M* = 10.56, controls, *M* = 11.48).

Summary of group differences in cognitive performance

In summary, with the exception of sensory SDRT performance, schizophrenic patients performed more poorly than controls on all cognitive measures. When the groups were equated for IQ, group differences were no longer significant. That is, schizophrenics' performance on the experimental cognitive measures was consistent with their overall level of intellectual functioning.

Volumetric MRI Measures

A summary of hemisphere, area 46, and planum measures for each group is provided in Table. A 2 (Group) x 2 (Hemisphere: right, left) ANOVA, with repeated measures for the hemisphere factor, revealed that the groups did not differ with respect to left and right area 46_c volume percentages (Right: schizophrenics, *M* = .92%, controls, *M* = .89%; Left: schizophrenics, *M* = .84%, controls, *M* = .84%). However, in both groups, the right area 46_c was proportionally larger than the left (Right, *M* = .91%; Left, *M* = .84%), $F(1, 44) = 4.24$, $p < .05$. There was no Group x Hemisphere interaction (see Table 4).

A 2 (Group) x 2 (Hemisphere) ANOVA, with repeated measures for the hemisphere factor, revealed that the groups did not differ with respect to left and right planum measures (see Table 4). For both groups, the left planum was significantly larger than the right (left, $M = 3.76$ cm^3; right, $M = 2.39$ cm^3), $F(1, 41) = 55.56$, $p < .0001$.

A 2 (Group) x 2 (Hemisphere: left, right) ANOVA with repeated measures for the hemisphere factor revealed that the groups did not differ in terms of total left or right hemispheric volumes (right, schizophrenics, $M = 638.78$ cm^3, controls, $M = 653.87$cm^3; left, schizophrenics, $M = 640.77$cm^3, controls, $M = 663.96$ cm^3) and the Group x Hemisphere interaction was not significant (see Table 4).

In summary, the present findings suggest that the schizophrenics in this study had regional and hemispheric brain volumes that were consistent with controls. Across groups, the right area 46, was larger than the left and the left planum temporale was larger than the right. The left and right whole hemisphere volumes generally were equivalent.

Correspondence of Symptoms and Cognitive Variables

Is working memory performance related to negative symptoms? If the negative symptoms of schizophrenia and working memory deficits result from the same underlying mechanisms, as we have suggested, we would expect to see a relationship between these variables. Pearson *r* correlations were conducted to test the hypothesis that severity of negative symptoms is positively related to performance errors on working memory tasks, but not related to performance on the PD task. It also was hypothesized that the relationship between working memory and negative symptoms would not be a function of IQ. That is, working memory was expected to have value over and above that of IQ in predicting negative symptoms. Furthermore, it was hypothesized that positive and disorganized symptoms would not be correlated with working memory performance as we believe these result from pathology of different brain regions. The following specific hypotheses were tested:

1. Increased errors on the SDRT and SOP tasks is associated with greater severity of negative symptoms.
2. Increased errors on the control task (i.e. phonemic discrimination) is not associated with greater severity of negative symptoms.
3. The relationship between working memory performance and negative symptoms can not be accounted for by global cognitive decline. That is, working memory performance has greater value than IQ in predicting negative symptoms.
4. Increased errors on the SDRT and SOP tasks is not associated with severity of positive or disorganized symptoms.

Three sets of analyses were performed for each cognitive measure. First, Pearson *r* correlations were performed on the schizophrenic and control groups combined. The rationale for this was that "negative symptoms" are not exclusive to schizophrenia; patients who are depressed also display negative symptoms and normal individuals demonstrate variability in behaviors such as affective expression and initiation of speech and social behaviors. Since we were interested in exploring the mechanisms underlying this *behavior*, it seems reasonable to examine these relationships across groups. The limitation of this approach is that the PANSS was designed to assess psychiatric symptomatology and as a result, it does not assess the range of "normal" functioning. Controls tend to obtain ratings of 1 (i.e. "normal functioning") on the individual scales resulting in floor effects. Because of this limitation, a second set of correlations was conducted to assess the relationships between these variables within the schizophrenic group alone. In the third set of analyses, FSIQ was controlled in a regression in order to determine the proportion of variance of negative symptoms specifically accounted for by working memory. It was expected that negative symptom scores would be associated with working memory performance in the combined group correlations as well as correlations within the schizophrenic group alone. Moreover, it was expected that performance on the memory SDRT and SOP tasks would be significantly associated with negative symptoms even when IQ was controlled in regressions. Table 9 provides a summary of Pearson *r* correlations between all symptom cluster scores and cognitive measures.

Symptom Clusters and IQ Performance

Across group correlations. Figures 9, 10, and 11 provide graphical representations of the relevant correlations. Across groups, intellectual functioning was strongly associated with negative symptom severity ($r = -.70$, $p < .0001$). Full scale IQ also was associated with positive ($r = -.50$, $p = .001$), but not as strongly as with negative symptoms. The relationship between IQ and disorganized symptoms, although statistically significant ($r = -.44$, $p = .004$), appears rather weak on the scatter diagram (see Figure 11). The significant correlation was likely driven by group differences on these measures.

Table 9

Pearson R Correlations Between Cognitive Measures and Symptom Clusters

	Symptom Cluster							
	Negative		Positive		Disorganized		General Psychopathology	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
	Combined Groups							
WAIS-R								
VIQ	70	000*	.41	008*	.36	.02**	-.57	000*
PIQ	01	000*	-.54	000*	.46	.003*	-59	000*
FSIQ	70	000*	-.50	001*	.44	.004*	62	000*
Memory SDRT								
Error Distance	.32	.04**	.20	.20	.25	11	.33	04**
Response Time	.39	.00	.22	10	32	04**	.35	02**
Sensory SDRT								
Error Distance	.05	75	01	95	04	78	.03	.83
Response Time	22	15	-.01	93	07	66	13	42
Verbal SOP errors	0.51	.001*	0 41	007*	0.36	02**	0.53	000*
Nonverbal SOP errors	0.5	.001*	0.29	0.06	0.28	0.08	0 50	.001*
Phonemic Discrimination errors	0.45	0.003*	0 19	0.24	0.27	0.09	0 36	0.02

Note. *Significant at $p < .01$ **Significant at $p < .05$

Table 9 continued

	Symptom Cluster							
	Negative		Positive		Disorganized		General Psychopathology	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
				Schizophrenic Group				
WAIS-R								
VIQ	40	06	36	10	30	17	.04	.85
PIQ	14	54	008	97	02	93	-08	73
FSIQ	32	13	.22	32	.20	.37	-02	93
Memory SDRT								
Error Distance	07	75	12	60	03	91	10	.66
Response Time	04	87	14	55	08	72	.07	74
Sensory SDRT								
Error Distance	-06	70	06	74	15	50	.07	74
Response Time	14	.53	.33	15	-13	58	-.08	70
Verbal SOP—errors	-0.04	0.86	-0.15	0.5	-0.14	0.53	0.03	0.9
Nonverbal SOP errors	0.01	0.96	-0.39	0.08	-0.24	0.29	0.02	0.92
Phonemic Discrimination—errors	0.27	0.22	-0.22	0.33	-0.01	0.97	0.07	0.76

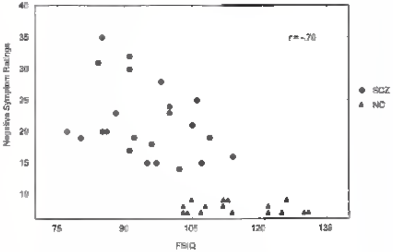

Figure 9. Full scale IQ vs negative symptom severity

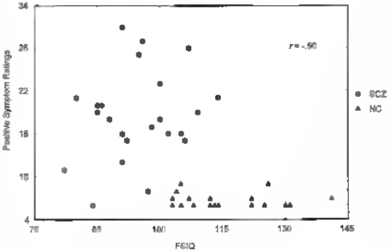

Figure 10. Full scale IQ vs. positive symptom severity

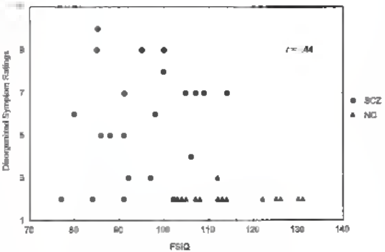

Figure 11. Full scale IQ vs disorganized symptom severity

Schizophrenic group analyses. Schizophrenic patients alone did not demonstrate any significant associations between symptom clusters and FSIQ. While group differences may, in part, account of the significant across group correlation, inspection of the scatter diagram suggests that negative symptoms may be related to IQ performance in at least a subgroup of patients. Within the schizophrenic group, the relationship between VIQ and negative symptoms approached significance ($r = -.40$, $p < .06$).

Symptom Cluster Scores and SDRT Performance

Error distance

Across group correlations. Contrary to our hypotheses, Pearson *r* correlations conducted across groups revealed minimal relationship between error distances on the memory SDRT task and severity of negative symptoms. As with previous correlations, the relationship between negative symptoms and memory SDRT error distance was statistically significant ($r = .32$, $p < .04$), but appeared to be driven by group differences and outliers. As expected, error distance on the sensory task was not associated with negative symptomatology. Neither error distance on the memory or sensory SDRT task was associated with positive or disorganized symptoms.

Schizophrenic group correlations. The schizophrenic group alone did not demonstrate significant relationships between error distance on the SDRT tasks and any of the symptom clusters.

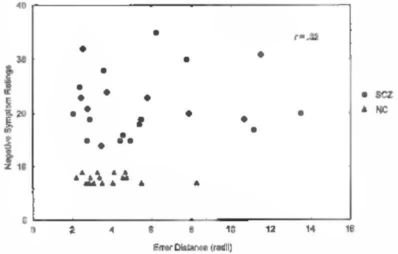

Figure 12. Memory SDRT error distance vs negative symptom severity
Error distance was measured as the distance of the touch response in terms of target radii, from the center of the target.

Regression controlling for FSIQ. In a regression analysis, controlling FSIQ, error distance on the memory SDRT task was not predictive of negative symptoms across groups ($pr = .04$, $p < .80$) or within the schizophrenic group alone ($pr = .14$, $p < .54$). Similarly, controlling for FSIQ, error distance on the sensory SDRT task was not predictive of negative symptoms across groups ($pr = .17$, $p < .26$) or among schizophrenic patients ($pr = .35$, $p < .11$).

Response times

Across group correlations. Combined group analyses revealed that slower response times on the memory SDRT task were not associated with more severe negative symptoms, a finding that contradicts our original hypotheses. Response times also were not associated with positive or disorganized symptoms. The Pearson r correlation between memory SDRT response time and severity of disorganized symptoms reached statistical significance ($r = .32$, $p = .04$), but examination of the scatter plot (see Appendix C, Figure C-1) suggested that this was largely due to a minority of patients ($n=3$) with extremely slow response times. Response times on the sensory task were not associated with any of the symptom clusters.

Schizophrenic group correlations. Schizophrenic patients alone did not demonstrate any relationships between SDRT performance and symptom severity.

Regression controlling for FSIQ. When FSIQ was controlled in a regression analyses, response times on the memory SDRT task did not predict negative symptoms across groups ($pr = .00$, $p < .99$) or within the schizophrenic group alone ($pr = .19$, $p <$

.39). Similarly, response times on the sensory SDRT task did not predict negative symptoms across groups ($pr = .14$, $p < .37$) or within the schizophrenic group ($pr = -.07$, $p < .76$).

Symptom Clusters and SOP Performance

Across group correlations. Figure 13 provides a graphical representation of the relationship between performance on the verbal SOP task and severity of negative symptoms. As predicted, Pearson r correlations conducted across groups revealed that more severe negative symptomatology was associated with higher percent errors on the verbal SOP task ($r = .51$, $p < .001$). Negative symptoms were not associated with nonverbal SOP performance. Although, the relationship between nonverbal SOP performance and negative symptoms was statistically significant ($r = .50$, $p < .001$), examination of the scatter plot in Figure C-2 (see Appendix C) reveals that this correlation seems to be driven by group differences and some extreme values within the schizophrenic group. Neither positive nor disorganized symptoms were significantly associated with nonverbal or verbal SOP performance. Again, while relationships between the severity of positive and disorganized symptoms and error rates on the verbal SOP task were statistically significant ($r = .41$, $p < .007$; $r = .36$, $p < .02$, respectively), these correlations were driven by group differences and do not appear to reflect a true linear relationship (see Figures C-3 and C-4 in Appendix C).

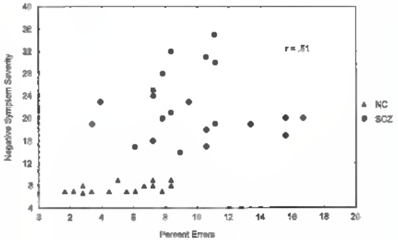

Figure 13. Mean verbal SOP percent errors vs. negative symptom severity

Schizophrenic group correlations. Within the schizophrenic group alone SOP performance was not associated with any of the symptom cluster scores. Examination of the scatter diagrams suggest that negative symptoms among schizophrenics may be associated with increased verbal SOP errors in a subgroup of schizophrenics The sample was too small to explore this possibility further

Regression controlling for FSIQ. When FSIQ was controlled in a regression analyses, SOP errors did not predict negative symptoms across groups ($pr = .03$, $p < .83$), or among schizophrenic patients In contrast to our hypotheses, when FSIQ was controlled, increased SOP errors tended to be associated with less severe negative symptoms ($pr = -.37$, $p < .09$)

Symptom Clusters and Phonemic Discrimination Performance

Across group correlations. Consistent with our hypotheses, error rate on the PD task was not associated with severity of negative symptomatology Across groups, the relationship was statistically significant ($r = .45$, $p = .003$) but appeared to be driven by a few outliers, Figure C 5 in Appendix C provides a graphical representation of the data When two outliers were removed, the relationship was not significant

Schizophrenic group correlations. When examined separately the schizophrenic group did not demonstrate a significant relationship between PD errors and any of the symptom clusters

Regression controlling for FSIQ. When FSIQ was controlled in a regression analyses, PD errors did not predict negative symptoms across groups ($pr = .07$, $p < .66$), or among schizophrenic patients ($pr = .11$, $p < .59$).

Summary of Correlations Between Symptom Clusters and Cognitive Performance

Across group results. Across group correlations only weakly support our initial hypotheses. Specifically, results of these analyses support our hypothesis that greater severity of negative symptoms is associated with poorer performance on the verbal SOP task, a test of working memory. This relationship appeared to be most representative of a small subgroup of patients. Contrary to expectations, performance on the memory SDRT task was not associated with negative symptomatology. As predicted, negative symptoms were not associated with performance on the sensory SDRT or PD tasks. Also consistent with our predictions, positive and disorganized symptoms were not associated with performance on the memory SDRT or SOP tasks. Importantly, full scale IQ was associated with all symptom clusters, but most strongly with negative symptoms. Contrary to our hypotheses, working memory performance did not have greater predictive value for negative symptoms than IQ.

These results weakly support our hypothesis that more severe negative symptoms are associated with impaired working memory. What seems to be most meaningful is a relationship between low IQ and more severe negative symptoms.

Schizophrenic group correlations and regressions. The schizophrenic group alone did not show any statistically significant relationships between working memory performance and negative symptoms. As mentioned above, examination of scatter diagrams suggest that a subgroup of patients demonstrate a relationship between more severe negative symptoms and poorer performance on a verbal working memory task. Failure to find significance could have been due to small sample size, and/or heterogeneity within the schizophrenic group.

Correspondence of Symptom Clusters and Volumetric MRI Measures

Is the size of area 46, related to negative symptoms? If the negative symptoms of schizophrenia result from pathology or lack of development of area 46, within the DLPFC, as we have suggested, we would expect to see a relationship between negative symptom severity and the neural structure area 46. In this case, we examined the gross volume of area 46. Pearson r correlations were conducted to test the hypothesis that smaller area 46, volumes would be related to greater severity of negative symptoms, but not positive or disorganized symptoms. It also was hypothesized that the size of a control brain region (i.e. planum temporale) would not be associated with negative symptoms. The following specific hypotheses were tested:

1. Smaller area 46, volumes, controlling for total brain volumes, will be associated with greater severity of negative symptoms.
2. Smaller size of the control brain region (i.e. planum temporale) will not be

associated with greater severity of negative symptoms.

3. Total brain volumes will not be predictive of negative symptomatology

4. Area 46_c volumes will not be associated with severity of positive or disorganized symptoms.

Two sets of analyses were performed for each brain measure. First, Pearson *r* correlations were conducted using data from the two groups combined. Second, a set of correlations was conducted to assess the relationships between these variables within the schizophrenic group separately. The rationale for these analyses was the same as that for examining the correspondence of cognitive measures and symptom clusters. In short, the separate correlations for the schizophrenic group were performed because spurious effects may occur when two distinct groups are combined in a correlational analysis. Moreover, the lack of variability of symptom ratings within the control group also may result in spurious effects. On the other hand, controls may display one end of a spectrum of behavior and for this reason, across group correlations may be informative.

Symptom Clusters and Area 46

Contrary to our hypotheses, right, left, and total area 46_c volumes were not associated with negative symptoms across groups or within the schizophrenic group alone. Area 46_c measures also were not associated with other symptom clusters.

Symptom Clusters and Planum Temporale

Left and right planum measures were not related to any of the symptom clusters across groups or within the schizophrenic group alone. Planum asymmetry, calculated by subtracting the surface area of the right planum from surface area of the left planum and dividing by the area of the left planum, i.e. (left planum - right planum)/left planum, also was not associated with any of the symptom clusters.

Symptom Clusters and Hemisphere Volumes

Pearson *r* correlations conducted across groups revealed that left, right, and total hemispheric volumes were not associated with negative, positive, or disorganized symptom clusters (see Table 10). Within the schizophrenic group larger right hemisphere volumes were associated with more severe disorganized symptoms ($r = .48$, $p < .02$).

Summary of Correlations between Symptom Clusters and Volumetric MRI Measures

Results of our analyses failed to support our hypothesis that smaller area 46 volumes would be associated with more severe negative symptoms. Area 46 and planum temporale measures were not associated with any of the symptom clusters. Larger total brain volumes among schizophrenic patients were associated with more severe disorganized symptoms, a finding that was not predicted.

Predicting Negative Symptom Scores from Area 46 Volumes and Cognitive Measures

According to our original hypotheses, it was expected that both area 46 measures and working memory performance would be predictive of negative symptom severity

Table 10

Pearson *r* Correlations between Brain Measures and Symptom Clusters

	Symptom Cluster							
	Negative		Positive		Disorganized		General Psychopathology	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
				Combined Groups				
Area 40								
Right	03	84	03	87	16	.31	01	.92
Left	-10	54	-06	72	.03	85	.05	72
Total	-,0	65	-02	90	09	56	.03	87
Planum Temporale								
Right	18	27	17	.29	-10	53	-13	42
Left	-.01	94	06	70	-05	75	-.08	63
Asymmetry	17	31	22	18	15	.34	11	49
Hemisphere								
Right	03	84	03	87	18	.31	92	,92
Left	10	,54	-,06	72	03	85	-.05	72
Total	.07	85	-.02	90	09	56	-03	87
				Schizophrenic Group				
Area 40								
Right	11	62	.27	22	10	64	.35	11
Left	18	41	11	61	-.03	.90	-.08	70
Total	.26	23	14	52	42	05	97	08
Planum Temporale								
Right	02	91	-03	90	08	73	10	64
Left	08	71	.05	81	04	85	-.27	22
Asymmetry	03	86	-004	98	02	92	23	28

Multiple regression analyses were conducted to explore whether, when considered together, these variables are predictive of negative symptoms. Four sets of analyses were conducted, one for each of the cognitive measures. Each set included regression analyses predicting negative, positive and disorganized symptoms across groups. Regressions involving negative symptoms also were conducted within the schizophrenic group alone. Finally, regressions predicting negative symptoms were conducted both with and without IQ entered into the models to explore the predictive value of other cognitive and brain variables in the absence of IQ scores.

Area 46, Memory SDRT, and FSIQ

Across group analyses

A multiple regression analysis including SDRT error distances, FSIQ, and left and right area 46_c volumes accounted for 52% of the variance of negative symptoms, $F(4, 41) = 11.25$, $r^2 = .52$, $p < .0001$. Full scale IQs and right area 46_c volumes contributed significantly to the model (FSIQ $pr = -.67$, $p < .0001$, right area 46, $pr = .33$, $p < .03$), low FSIQ and large right area 46_c volumes predicted more severe negative symptoms. Left area 46_c volume was a marginally significant predictor: smaller left area 46_c volumes were associated with more severe negative symptoms ($pr = -.28$, $p < .07$). Error distance on the memory SDRT task did not contribute to the predictive value of the model. When FSIQ was removed from the original equation, the model was no longer significantly predictive of negative symptoms, $F(3, 42) = 1.99$, $R^2 = .12$, $p < .13$. Error distance on the SDRT task was a significant predictor of negative symptoms ($pr = .32$, $p < .03$), increased error distance was related to greater severity of negative symptoms. Right and left area 46_c volumes were not significant predictors.

Similar results were obtained in a regression analysis predicting positive symptoms. Error distance on the memory SDRT task, FSIQ, left area 46_c and right area 46_c volumes accounted for 34% of the variance of positive symptoms, $F(3, 38) = 4.85$, $R^2 = .34$, $p < .003$. Full scale IQS and right area 46_c volumes contributed significantly to the model (FSIQ $pr = -.32$, $p < .001$, right area 46 $pr = .33$, $p < .04$). low FSIQ and large right area 46_c volumes predicted more severe positive symptoms.

With regard to disorganized symptoms, error distance on the memory SDRT task, FSIQ, left area 46_c and right area 46_c volumes accounted for 23% of the variance, $F(4, 37) = 2.75$, $R^2 = .24$, $p < .04$. Full scale IQ was the only significant predictor ($pr = -.40$, $p < .01$).

Schizophrenic group analyses

Within the schizophrenic group, area 46_c volumes, memory SDRT error distance, and FSIQ did not account for a significant portion of the variance of negative symptoms. Greater severity of negative symptoms was associated with lower FSIQ ($pr = -.46$, $p < .04$). Area 46_c volumes and SDRT error distances did not contribute to the model. When FSIQ was removed from the original model, left and right area 46_c volumes and SDRT error distance did not predict negative symptom ratings, $F(3, 19) = .56$, $R^2 = .08$, $p < .66$.

Area 46, Sensory SDRT, and FSIQ

Across group analyses

A multiple regression analysis including sensory SDRT error distances, FSIQ, and left and right area 46_v volumes accounted for 53% of the variance of negative symptoms, $F(4, 41) = 11.68$, $R^2 = .53$, $p < .0001$. Full scale IQs and right area 46_v volumes contributed significantly to the model (FSIQ $pr = -.72$, $p < .0001$; right area 46_v $pr = .31$, $p < .04$): low FSIQ and large right area 46_v volumes predicted more severe negative symptoms. Left area 46_v volume was a marginally significant predictor: smaller left area 46_v volumes were associated with more severe negative symptoms ($pr = -.28$, $p < .07$). Performance on the sensory SDRT task did not contribute to the predictive value of the model. When FSIQ was removed from the original equation, the model was no longer significantly predictive of negative symptoms, $F(3, 42) = .40$, $R^2 = .03$, $p < .75$. None of the individual variables were significant predictors.

With regard to predicting positive symptoms, error distance on the sensory SDRT task, FSIQ, left area 46_v and right area 46_v volumes accounted for 42% of the variance of positive symptoms, $F(3, 38) = 6.94$, $R^2 = .46$, $p < .001$. Full scale IQ was the only significant predictor ($pr = -.64$, $p < .001$).

Similarly, with regard to disorganized symptoms, error distance on the SDRT task, FSIQ, left area 46_v and right area 46_v volumes accounted for 23% of the variance, $F(4, 37) = 2.75$, $R^2 = .23$, $p < .04$. Full scale IQ was the only significant predicter ($pr = -.46$, $p < .003$).

Schizophrenic group analyses

Within the schizophrenic group, area 46$_c$ volumes, sensory SDRT error distance and FSIQ together in a regression model were not predictive of negative symptoms, $F(4, 18) = 2.06$, $R^2 = .31$, $p < .13$. Full scale IQ was a significant predictor of negative symptoms ($pr = -.50$, $p < .02$), however, the other variables did not add predictive value to the model. When FSIQ was removed from the original model, left and right area 46$_c$ volumes and sensory SDRT error distance did not predict negative symptom ratings, $F(3, 19) = .54$, $R^2 = .08$, $p < .66$.

Area 46, SOP, and FSIQ

Across group analyses

Together, SOP errors, FSIQ, and left and right area 46$_c$ volumes accounted for 52% of the variance of negative symptoms, $F(4, 41) = 11.16$, $R^2 = .52$, $p < .0001$. Full scale IQS and right area 46$_c$ volumes contributed significantly to the regression model (FSIQ $pr = -.51$, $p < .004$, right area 46 $pr = .33$, $p < .04$); low FSIQ and large right area 46$_c$ volumes predicted more severe negative symptoms. Left area 46$_c$ volume was a marginally significant predictor; smaller left area 46$_c$ volumes were associated with more severe negative symptoms ($pr = -.27$, $p < .08$). Performance on the SOP task did not contribute to the predictive value of the model. When FSIQ was removed from the original equation, the model continued to be significantly predictive of negative symptoms, $F(3, 42) = 7.52$, $R^2 = .59$, $p < .0003$. Errors on the SOP task contributed significantly to the model (*pr* = .58 $p <$ 0001) and right area 46_c volumes contributed marginally (*pr* = .28 $p <$ 06)

Similar results were obtained in a regression analysis predicting positive symptoms. Errors on the SOP task FSIQ left area 46 and right area 46_c volumes accounted for 33% of the variance of positive symptoms, $F(4\ 38) = 4\ 68$ $R^2 = .57$ $p <$ 003 Full scale IQ and right area 46_c volumes contributed significantly to the model (FSIQ *pr* 36 $p <$ 02, right area 46_c *pr* = 32, $p < .04$), low FSIQ and large right area 46_c volumes predicted more severe positive symptoms.

With regard to disorganized symptoms error distance on the sensory SDRT task, FSIQ left area 46, and right area 46_c volumes accounted for 23% of the variance, $F(4, 37)$ = 2.75 $R^2 =$ 23 $p <$ 04 Full scale IQ was a marginally significant predictor (*pr* = -.30 $p < .06$). None of the other variables were significant predictors of disorganized symptoms

Schizophrenic group analyses

Within the schizophrenic group, area 46_c volumes, SOP errors and FSIQ did not account for a significant portion of the variance of negative symptoms, $F(4, 18) = 2\ 15$, R^2 32 $p <$ 12 Greater severity of negative symptoms was associated with lower FSIQ (*pr* = -.51 $p <$ 02) however area 46_c volumes and SOP errors did not contribute to the model When FSIQ was removed from the original model the remaining variables (left and right area 46_c volumes, SOP errors) did not predict negative symptom ratings, $F(3, 19) = .55$, $R^2 =$ 08 $p <$ 66

Area 46, PD, and FSIQ

Across group analyses

A multiple regression analysis including sensory PD errors, FSIQ, and left and right area 46_g volumes accounted for 52% of the variance of negative symptoms, $F(4, 41) = 11.27$, $R^2 = .52$, $p < .0001$. Full scale IQS and right area 46_g volumes contributed significantly to the model (FSIQ, $pr = -.61$, $p < .0001$; right area 46, $pr = .32$, $p < .03$). Low FSIQ and large right area 46_g volumes predicted more severe negative symptoms. Left area 46_g volume was a marginally significant predictor; smaller left area 46_g volumes were associated with more severe negative symptoms ($pr = -.27$, $p < .08$). Performance on the PD task did not contribute to the predictive value of the model. When FSIQ was removed from the original equation, the model continued to be significantly predictive of negative symptoms, $F(3, 42) = 4.17$, $R^2 = .23$, $p < .01$. Errors on the PD task was the only significant predictor in the model ($pr = .45$, $p < .002$).

Similar results were obtained in a regression analysis predicting positive symptoms. Errors on the PD task, FSIQ, left area 46, and right area 46_g volumes accounted for 36% of the variance of positive symptoms, $F(4, 38) = 5.43$, $R^2 = .36$, $p < .001$. Full scale IQS and right area 46_g volumes contributed significantly to the model (FSIQ, $pr = -.56$, $p < .001$; right area 46, $pr = .32$, $p < .04$): low FSIQ and large right area 46_g volumes predicted more severe positive symptoms.

With regard to disorganized symptoms, errors on the PD task, FSIQ, left area 46, and right area 46_g volumes accounted for 23% of the variance, $F(4, 37) = 2.75$, $R^2 = .23$, $p < .04$. Full scale IQ was the only significant predictor ($pr = -.38$, $p < .02$).

Schizophrenic group analyses

Within the schizophrenic group, area 46_v volumes, PD errors and FSIQ did not account for a significant portion of the variance of negative symptoms $F(4, 18) = 1.28$, $R^2 = .22$, $p < .31$. None of the variables were significant predictors of negative symptoms. When FSIQ was removed from the original model, the remaining variables (left and right area 46_v volumes, SOP errors) did not predict negative symptom ratings, $F(3, 19) = 1.14$, $R^2 = .15$, $p < .009$.

Summary of Regression Analyses

Regression analyses conducted across groups support our hypothesis that working memory and area 46_v volumes are significant predictors of negative symptoms. Together, low FSIQ and *large* right area 46_v volumes predicted more severe negative symptoms. This finding contradicts our original hypothesis that *smaller* area 46_v volumes would be associated with more sever negative symptoms. However, it is possible that an abnormality of area 46_v could take the form of larger volume. Larger regional brain volumes may result from disruption to the normal pruning process during development or excessive cell proliferation. Notably, FSIQ was the strongest predictor and area 46_v volumes added additional predictive value. Because of the considerable shared variance between working memory measures and FSIQ, working memory did not add predictive value over and above FSIQ. However, working memory measures were predictive of negative symptoms when IQ was not included in the model. Also consistent with our hypotheses sensory SDRT performance was not a significant predictor of negative symptoms; however contrary to expectations phonemic discrimination predicted negative symptoms.

Working memory measures were not predictive of positive or disorganized symptoms a finding consistent with our hypotheses. Contrary to our hypotheses, however area 46_v volumes were predictive of positive symptoms when considered with FSIQ Area 46_v measures did significantly predict disorganized symptoms

Within the schizophrenic group, the only variable that predicted negative symptom severity was FSIQ Area 46_v volumes and performance on the other cognitive tasks were not significant predictors of negative symptoms.

DISCUSSION

The present study addressed the question of what brain mechanisms are involved in producing the negative symptoms of schizophrenia. The working hypothesis was that functional and/or structural pathology of the DLPFC area 46 in particular is associated with the negative symptoms observed in schizophrenia. This hypothesis was based on clinical observations and animal lesion studies that suggested that damage to the DLPFC results in symptoms consistent with negative symptoms (Stuss & Benson, 1986, Goldman-Rakic, 1987). Notably animal and human lesion studies as well as functional imaging studies have implicated the medial frontal cortex and anterior cingulate as being important for internal generation of responses (Damasio & Anderson, 1993 Passingham, 1993 Picard and Strick, 1996) Thus, an alternative hypothesis is that negative symptoms are related to pathology of the medial frontal cortex

Negative symptoms have been described by Frith (1992) as a deficit of "willed action" which he defined as an inability to guide behavior based on internal motivations and cues. This definition of "willed action" is consistent with Goldman Rakic s (1987) definition of working memory and Passingham s (1993) description of the functions associated with DLPFC areas 46 and 9 Because initiation of social behaviors spontaneous affect, and speech are, for the most part, internally driven, an impairment of "willed action" could disrupt these behaviors resulting in negative symptoms. This study was designed to test the hypothesis that negative symptoms are related to DLPFC pathology.

We approached this problem in two ways. First, we examined the functional integrity of area 46 by administering tests that have been found to be sensitive and specific to area 46 damage in non human primates (Goldman-Rakic, 1987; Petrides 1991b). These tests also have been implicated as showing functional specificity corresponding to area 46 in human functional imaging studies (McCarthy et al., 1994 Petrides et al., 1993b). Second, we assessed the structural integrity of this brain region by measuring its volume on MRI scans. We then examined the relationships between negative symptoms and the cognitive and structural brain variables measured. In doing so, we addressed three broad questions: 1) Is working memory performance related to negative symptoms? 2) Is the size of area 46, related to negative symptoms? 3) Are there group differences between schizophrenic patients and controls that may reflect an underlying process that is common to all forms of schizophrenia? Each of these questions are addressed below, followed by discussions of general methodological considerations as well as directions for future research.

The Relationship Between Working Memory and Negative Symptoms

Is working memory performance related to negative symptoms? The present findings only weakly support our hypotheses: within a subgroup of patients, greater severity of negative symptoms was related to poorer performance on one of the three working memory measures (i.e., verbal SOP). Positive and disorganized symptoms also were not related or were related to a lesser degree to verbal working memory performance. Consistent with our hypotheses, negative symptoms were not associated with performance on the two control tasks which did not require working memory.

Negative symptoms were significantly related to IQ scores: lower VIQ, PIQ, and FSIQ were associated with more severe negative symptoms. Contrary to our predictions, when IQ was partialled out in the analyses, verbal working memory performance was no longer a significant predictor of negative symptom severity. Intellectual performance also accounted for some of the variance for positive and disorganized symptoms, but these relationships were not nearly as strong as the relationship between IQ and negative symptoms. Other investigators also have reported associations between negative symptoms and general cognitive dysfunction (Addington, Addington, & Maticka-Tyndale, 1991; Crow, 1980; Strauss et al., 1974), while some report a specific relationship between negative symptoms and working memory (Fleming et al., 1995; Stolar et al., 1995). Stolar (1992) found that the negative symptom alogia, but not positive symptoms, was associated with poorer performance on controlled oral word association; however, this effect failed to reach significance when IQ was partialled out in the analysis. Thus, it appears that negative symptoms may be associated with impaired working memory, but that general cognitive functioning is a more critical factor and may be a predictor of both negative symptoms and impaired working memory. Alternatively, it is possible that impaired working memory and low general intellectual functioning together contribute to negative symptomatology.

Importantly, based on statistical significance in the across group analyses, one could conclude that negative symptoms are associated with performance on working memory tasks, phonemic discrimination, and intellectual functioning. However, examination of scatter diagrams reveals that these correlations were largely spurious and based on group differences on cognitive and symptom measures. This is important in the sense that correlations reported by other groups of investigators may also appear to be stronger than they are if only the numerical values of the correlations are reported. This is true even in the within group analyses when there is heterogeneity within the group and/or extreme outliers.

The initial premise of this study was that negative symptoms would be associated with impaired working memory because working memory is an important component of response production. A failure to produce behaviors (i.e., negative symptoms) may be a result of poor motivation or lack of internal drive to respond. Alternatively, failure to produce behavior may be a result of inability to organize thoughts and behaviors well enough to produce a response. Damage to the DLPFC has been associated with many deficits including intentional disorders, motor impersistence, apathy, and deficits in strategy formation and planning (Heilman & Watson, 1991; Stuss & Benson, 1986). Medial prefrontal damage also has been associated with impaired intention, akinesia, and abulia (Heilman & Watson, 1986; Damasio & Anderson, 1993). Importantly, the DLPFC is connected with medial prefrontal regions and these two regions likely work together to produce intentional or internally driven responses. Given that negative symptoms were not highly associated with working memory performance, it is possible that negative symptoms are more strongly related to medial prefrontal pathology. Furthermore, given the organization deficits that occur with DLPFC, one could hypothesize that damage in this regions would be more associated with disorganization symptoms. Our findings do not support the latter hypothesis. To our knowledge there are no studies that have specifically explored the relationship between medial prefrontal pathology and negative symptoms.

Correlations between the cognitive measures used in this study raise questions about the nature of the relationship among IQ and working memory measures. Examination of the data revealed that IQ, SOP, SDRT, and PD are all highly correlated with one another across groups and within the schizophrenic group. The only cognitive variable that was not related to any other, including IQ, was sensory SDRT performance. Other investigators have reported a similar correlation between IQ and working memory or executive functions (Goldberg et al., 1990; Morice & Delahunty, 1996). Morice and Delahunty (1996) hypothesized that this relationship can be accounted for by the deleterious effect impaired working memory has on intellectual performance. Interestingly, controls did not show strong associations among cognitive variables. It is possible that schizophrenics rely on different strategies for completing cognitive tasks than controls. There is some indirect support for this hypothesis at least with regard to SOP performance. Following completion of this task, all participants were asked what strategies they used to remember the stimuli. Controls generally described more elaborate strategies than patients. It is possible that schizophrenic patients rely on less effective strategies than controls on complex tasks and that this problem affects them across tasks.

If lower IQ scores are a result of impaired working memory performance, as suggested by Morice and Delahunty (1996), we would expect subtests from the WAIS-R that require working memory (Digit Span, Digit Symbol, Picture Arrangement, Block Design) to be more related to performance on our specific measures of working memory than those that do not. Post hoc examination of the current data did not support this prediction. Better performance on all eleven subtests of the WAIS-R was related to better performance on the SOP task and 10 of 11 subtests were related to memory SDRT performance. Thus, the relationship between FSIQ and negative symptoms does not appear to be the result of a specific deficit in working memory. It is possible that negative symptoms are a result of diffuse cognitive dysfunction or a common underlying processes that disrupts both intellectual performance and working memory. Alternatively, working memory may not be as well localized in humans as it is in monkeys. That is, it may be a more critical aspect of many different human cognitive and behavioral functions than is commonly thought. This issue is discussed further in Methodological Considerations.

Results of across group analyses should be tempered in light of group differences on cognitive and symptom measures. Within the schizophrenic group alone, relationships between negative symptoms and cognitive performance were considerably weakened and were not statistically significant. This may have been due to our small sample size and/or heterogeneity within the schizophrenic group. Despite the inconsistencies in these findings, examination of the scatter diagram in Figure 9 suggest that individuals with low IQ and poor performance on the verbal SOP task tend to have more severe negative symptoms

In summary, one primary hypothesis -- that negative symptoms are specifically associated with DLPFC dysfunction, as measured by tests of working memory, was only weakly supported Based on the current findings we can conclude that negative symptoms are related to low general intellectual functioning and impairment on at least one verbal working memory task These relationships appear to be relatively specific in light of findings that positive and disorganized symptoms were very weakly associated with intellectual performance Results of significant relationships between IQ, working memory, and negative symptoms indicate no clear pattern of focal or systemic brain dysfunction associated with negative symptoms This point is highlighted by our failure to find bivariate associations between volumetric MRI measures and negative symptoms This point is discussed further below

The Relationship Between Area 46, Volume and Negative Symptoms

Is the size of area 46, related to negative symptoms? The hypotheses that smaller area 46, volumes would be associated with negative symptom severity was not supported by results of bivariate correlational analyses Volumetric brain measures, including the sizes of area 46, plana temporale, total brain and hemispheres, were not associated with ratings on any of the symptom clusters Other studies that examined measures of estimates of total prefrontal volumes also have failed to find relationships between prefrontal volumes and negative symptoms (Andreasen et al., 1986, Bilder et al., 1995, Raine et al., 1992, Wolkin et al., 1992). The failure to find strong relationships between DLPFC and negative symptoms contradicts Blumer and Benson's (1975) model of psuedodepression. As such, it will be important to examine other brain regions that have been found to be involved in response selection and intention to respond, such as the anterior medial frontal cortex (pre-supplementary motor area and anterior cingulate), the thalamus, and the straitum (Passingham, 1993; Picard & Strick, 1996). While abnormalities within the globus pallidus have been reported (Early et al., 1987, Bogerts et al., 1985), the relationship between globus pallidus abnormalities and negative symptoms has not been delineated. Additionally, Damasio and Anderson's (1993) conceptualization of the role of medial prefrontal cortex in intentional behavior seems particularly relevent to negative symptoms. To this date, there do not appear to be any MRI studies that have explored the hypothesis that negative symptoms are associated with medial frontal pathology.

The prediction that smaller area 46_c volumes would be associated with poorer performance on measures of working memory also was not supported. In fact, none of the brain measures was associated with performance on any of the cognitive tests employed. A failure to find a relationship between area 46_c and working memory performance raises questions because this region has been implicated in working memory in both animal lesion studies (Goldman-Rakic, 1987) and human functional imaging studies (Jonides et al., 1993, McCarthy et al., 1994). Other investigators also have failed to find significant relationships between structural prefrontal measures and putative prefrontal functions (Andreasen et al., 1986; Bilder et al., 1995; Raine et al., 1992). Seidman et al. (1994) found strong correlations between DLPFC volumes and performance on a large number of neuropsychological test; however, when adjusted for whole brain volumes these findings no longer reached significance, with the exception of one measure of attention. It may be that working memory is not as well localized in humans as it is in animals. Functional imaging studies do not strongly support the specific role of the DLPFC in working memory. Using PET imaging, increased rCBF has been identified in the anterior cingulate cortex during performance of working memory tests and tasks that require internal generation of responses (Petrides, Alivisatos, Evans, & Meyers, 1993; Picard & Strick, 1996). Furthermore, Bilder et al. (1995) found a correspondence between prefrontal functioning and anterior hippocampal but not prefrontal volumes. These authors interpreted their findings as supporting abnormal development of the fronto-hippocampal system. They suggested that gross structural deficits are more apparent in the hippocampus because of its relatively fewer layers and smaller size. Differential vulnerability of regions within the neural network associated with working memory processes may account for the strong behavioral correlates of area 46_v volumes were not found in the present study.

Methodological variables also may account for the failure to find an association between area 46_v and working memory. First, it is possible that the volume of a particular structure may be normal while the functioning of that structure is impaired. If, for example, neurotransmitter systems or structures projecting to area 46 are impaired, area

46 will not function optimally because it is acting on aberrant input. Given that area 46 is only one part of larger working memory and/or attentional network, impairment in any of a number of regions may result in impaired functioning which would not be reflected in area 46 volumes. In future studies it will be necessary to examine the larger brain system involved in working memory, as opposed to isolated structures, in order to determine what specific brain regions/systems are involved. Area of potential relevance include parietal cortices, medial temporal regions, the striatum, and the dorsomedial thalamus. In fact animal lesion studies have identified working memory deficits in animals following lesions of the dorsomedial nucleus of the thalamus (Isserhoff et. al, 1982). Functional imaging techniques could also be used to assess the functional integrity of the DLPFC during working memory performance. Even if the pathology is not within the DLPFC itself, functional imaging could reveal dysfunction in the prefrontal cortex as a result of abnormal afference. It also is possible that subtle pathology in area 46 exists, but that it is not detectable in gross volumetric measures. For example, in a postmortem study Selemon et. al (1995) found that schizophrenic patients had fewer large pyramidal neurons and more medium and small neurons in the prefrontal cortex than controls. Volumetric MRI measurements may not be sensitive enough to detect such differences. Evaluation of tissue densities on structural MRI and functional imaging may be more useful in this regard. Alternatively, developmental abnormalities may be apparent in abnormal gyral patterns which could be examined on structural MRI. Finally, negative symptoms reflect a failure to initiate some highly complex behaviors that may be dependent on multiple brain systems. It is possible that area 46 is part of one of the

systems involved, but that other variables also are involved and possibly interact with area 46 pathology in predicting negative symptoms. Finally, it is possible that the measurement methods used did not adequately measure the actual structure of interest. This issue of validity is discussed in further detail in Methodological Considerations.

In the present study area 46_c volumes alone were not significantly predictive of negative symptomatology; however, when considered with IQ, larger right area 46_c volumes accounted for a significant portion of the variance of negative symptoms. Right area 46_c volumes also predicted positive symptoms when considered with IQ; however, this relationship was not as strong as that with negative symptoms. Disorganized symptoms were not associated with area 46_c volumes. The relative specificity of the relationship between right area 46_c volumes and negative symptoms suggests that area 46_c may be involved in production of negative symptoms, but that it is not a simple bivariate correlation.

In summary, area 46_c volumes alone were not predictive of negative symptomatology and also were not associated with performance on working memory measures. On the other hand, right area 46_c volume, when considered with IQ performance in a regression, was a significant predictor of negative symptoms. It is unclear at this time whether the failure to find bivariate correlations between the volume of area 46_c and behavioral measures was due to methodological and/or theoretical problems with the MRI measurements or because its relationship to negative symptoms is too complex to identify with this level of analysis.

Group Differences

Are there Group Differences Between Schizophrenic Patients and Controls that Reflect an Underlying Process that is Common to All Forms of Schizophrenia? This question was exploratory in nature, because, as previously addressed, schizophrenics are a heterogeneous group and the purpose of this study was to examine the relationships between specific symptoms and regional brain pathology. Nonetheless, group differences were explored in order to assess the consistency between the current findings and other studies. Moreover, examining group differences allows us to remain open to the possibility that, despite extreme heterogeneity of symptoms, there might be an underlying brain process that is common to all forms of schizophrenia. Two main questions were addressed, (a) Do schizophrenics perform more poorly than controls on working memory measures? (b) Is area 46, smaller in schizophrenic patients compared to controls?

Do Schizophrenics Perform More Poorly than Controls on Working Memory Measures?

If so, is this finding specific, or the result of diffuse cognitive dysfunction? The results of the spatial delayed response task indicate that spatial working memory is significantly impaired in schizophrenics as a group. Although both groups performed more poorly and were slower in responding on the memory compared to the sensory version of this task, schizophrenics were much more vulnerable to the delay with distraction than controls. The impaired performance of schizophrenics on the memory task can not be accounted for by simple visual perceptual or motor problems as the schizophrenic group performed as well as controls on the sensory task. The memory and sensory versions of this task were identical with one exception. In the memory task the subject was required to hold an internal representation of the target stimulus in mind over an 8 second delay while performing a distraction task. In the sensory task there was no delay with distraction; the subject was signaled to respond immediately. Therefore working memory was not required during the sensory task. Even when the groups were equated for IQ by means of an ANCOVA, the schizophrenic group showed greater vulnerability than controls to the delay with distraction. Similar results have been reported by other investigators (Carter, Robertson, Nordahl, Chaderjian, Kraft, &O'Shora-Celaya, 1996; Keefe et. al., 1995; Park & Holzman, 1992). For example, Park and Holzman (1992) reported that schizophrenic patients performed more poorly than controls on both visual (oculomotor) and haptic (manual) spatial delayed response tasks. The present findings differed from previous studies in that in the present group of schizophrenic patients performed as well as controls on the sensory version of the task, which did not impose a delay.

There have been reports of normal performance by schizophrenics on other tasks such as the digit span subtest of the WAIS-R, controlled oral word association, dichotic listening, and finger sequence repetition (Park & Holzman, 1992, Raine et al., 1992). In our laboratory, however, schizophrenic individuals have generally been impaired on digit span and controlled oral word association. One variable that differentiates the current patient group from those that reported normal Digit Span scores is that the patients who participated in the present study were more chronic i.e. have had a longer length of illness and are quite disabled

Working memory impairments in schizophrenia are not restricted to spatial information; representational memory for self generated responses to abstract visual and verbal stimuli also was found to be impaired in the present study On the SOP task, schizophrenics, as a group, made more errors than controls however, this overall group difference may have been in part, related to global cognitive impairment as the main effect of group was no longer significant when FSIQ was controlled Other investigators have reported impairments in verbal working memory and other executive functions such as forward planning and set shifting (Morice & Delahunty 1996, Fleming, Goldberg Gold, & Weinberger 1995) Morice and Delahunty (1996) and Fleming et al. (1995) found that short term memory (e g digit span) with minimal distraction appears to be intact in schizophrenic patients, but that performance declined substantially more than in controls when even low level distraction was invoked They interpreted their findings as indicating that a component of working memory the central executive of working memory (Baddeley 1990), which has a limited capacity and is important for allocating attentional resources is impaired in schizophrenia. These authors did not control for IQ or global cognitive functioning, thus, the specificity of their findings is not certain. It is possible that the cognitive deficits experienced by schizophrenic patients was not specific to working memory, but could have resulted from more diffuse cognitive impairments

The possibility of more diffuse cognitive impairment in schizophrenia is supported by the finding that in addition to working memory deficits schizophrenic patients demonstrated impaired phonemic discrimination and lower IQ scores relative to controls. As with the SOP task, the group difference on the PD task was no longer significant when the groups were equated for IQ. Poorer phonemic discrimination was significantly associated with lower IQ scores and poorer performance on both working memory tasks. Similar findings of relatively low IQ and diffuse cognitive impairment have been reported by other investigators (Morice & Delahunty, 1996; Saykin et al., 1991).

The finding that negative symptoms were associated with greater cognitive impairment than positive and disorganized symptoms suggests that patients with different symptoms of schizophrenia have different cognitive deficits. The specific cognitive deficits associated with specific symptoms or symptom clusters could not be determined based on the current findings.

In summary, this group of schizophrenic patients were impaired on a variety of cognitive tasks regardless of symptomatology. They were not impaired across all cognitive domains as they performed normally on a simple spatial location task.

Is Area 46, Relatively Smaller in Schizophrenic Patients Compared to Controls?

Schizophrenic patients could not be differentiated from controls in terms of area

Previous volumetric MRI studies have reported inconsistent findings with regard to total and regional brain volumes. Some investigators have found no differences between schizophrenic patients and controls on measures of total brain volume (Kelsoe et. al 1988, Andreasen et. al., 1990, Young et. al., 1991, Breier et. al., 1992, Buchanan et. al., 1993) cortical volume (Chakos et. al., 1994) prefrontal volumes (Kelsoe et. al., 1988) or size and symmetry of the planum temporale (Kulynych, Vladar, Fantie, Jones, & Weinberger, 1995). Others have reported decreased cerebral (Andreasen et. al., 1986, Gur et. al., 1994, Andreasen et. al., 1995) and prefrontal volumes (Breier et. al., 1992, Harvey et. al., 1993, Schlaepfer et. al., 1994, Andreasen et al., 1995) as well as abnormal lateralization of the planum temporale (Hoff et. al. 1994, Petty et al., 1995, Rossi et al. 1992).

Because there is considerable inter- and intra-individual variability of schizophrenic symptoms a failure to find group differences in brain measures is not entirely unexpected. It has been difficult to identify group differences that are consistent from study to study, especially with the limited number of patients normally sampled. Differences in sample selection also may account for the variable findings reported in imaging studies. While some investigators limit their sample to first episode schizophrenics, others report findings from chronic schizophrenic patients. Differences in handedness of the study sample also may account for differences in MRI findings. Additionally, some patient groups are medicated while others are not. Neuroleptic medications include a wide range of typical and atypical antipsychotic agents, anxiolitics anticholinergics, and antidepressants which may affect the brain differentially

Methodological differences in MRI protocols and measurement methodologies also may account for inconsistent findings.

This is the first study that has specifically examined the size of area 46, using volumetric MRI. Others have used gross measures of prefrontal regions and have found decreased prefrontal and DLPFC volumes (Andreasen et al., 1986; Breier et al., 1992; Harvey et al., 1993; Raine et al., 1992), but these findings have not been replicated (Kelsoe et al., 1988; Wible et al., 1995). This discrepancy may be due to the different methodologies these groups of investigators used to measure prefrontal size.

Methodological Considerations

Correlational Studies

One of the problems encountered in correlational studies is difficulty in attribution of causality. In the present study, for example, we found an association between poor cognitive performance and negative symptoms. The relationship between these cognitive and symptom variables may reflect an underlying brain pathology that produces cognitive deficits that, in turn, produce behavioral deficits (i.e. negative symptoms). Alternatively, an underlying brain pathology may produce both cognitive deficits and negative symptoms, but the cognitive and negative symptoms may be independent from each other in the sense that one is not produced by the other. Finally, it may be the case that psychiatric symptomatology interferes with cognition, thus, causing poor performance on various cognitive measures. Determining the direction of causality is difficult because we do not have non invasive ways of debilitating selective brain systems and observing the behavioral effects. However, one way to approach this problem would be to measure cognitive functioning in groups of non-schizophrenic individuals who display behaviors similar to the negative features of schizophrenia. If the symptoms interfere with cognition regardless of diagnosis, we would expect to see such individuals perform similarly to schizophrenic patients with negative symptoms. If, on the other hand, these individuals do not demonstrate a similar pattern of cognitive deficits, we may infer that the cognitive deficits observed in schizophrenics with negative symptoms are not *caused* by their negative symptoms.

Symptom Measures

One methodological problem with the present study and others that evaluate psychiatric symptomatology is that there are floor effects for normal individuals on symptom rating scales. That is, normal individuals rarely display actual symptoms of schizophrenia and therefore receive ratings of 1 (i.e. normal functioning) on most of the subscales of the PANSS. Thus, there is little variability in ratings of their behavior to correlate with other behavioral (i.e. cognitive) measures. This is problematic if one's goal is to investigate regional brain pathology associated with certain behavioral manifestations as opposed to certain diagnoses. One might argue that if symptoms are related to certain cognitive deficits, normal individuals should not demonstrate much variability in their cognitive performance either. Indeed they do not demonstrate as much variability as schizophrenic patients. Normal individuals do, however, vary in their performance on these tasks and social behaviors do vary between normal individuals in a manner not captured by the PANSS scale. The symptom rating scales used are simply not designed to measure "normal" variability. For example, blunted affect is a negative symptom of schizophrenia. It is characterized by limited behavioral expression of emotion. Although the range of affective expression in psychiatric patients may be greater than that in normal individuals, normal individuals do vary in their degree of affective expression. Some scales are available for identifying Schizotypal Personality Disorder (Eckblad & Chapman, 1983; Chapman & Chapman, 1987) which measure such behaviors along a continuum with a wider margin for normal behavior than schizophrenia scales offer. These scales include subscales (e.g., magical thing, physical anhedonia, social anhedonia) that are meant to parallel the symptom clusters that have been identified in schizophrenia (Eckblad & Chapman, 1983; Chapman & Chapman, 1987). While these measures may be useful for characterizing a wider range of behaviors in normals, the use of these scales with schizophrenic patients needs to be further evaluated.

Cognitive Measures

In the present study two tasks were used to measure working memory performance in schizophrenic individuals and controls. These tasks were chosen because of evidence from animal lesion studies and human lesion and functional imaging studies that they are sensitive and specific to functioning of area 46 within the DLPFC. We avoided using standard measures of "prefrontal functions" such as the WCST and COWA, because although they are often sensitive to prefrontal damage, impairments on these tasks have been observed in conjunctions with lesions outside of prefrontal cortex (Anderson et al., 1991; Stuss & Benson, 1986). However, the present results suggest that the tests we used may not be as functionally specific as we assumed, at least in the present population. Working memory performance was strongly related to intellectual functioning and was even associated with phonemic discrimination. Addington et al. (1991) applied factor analysis to their data and found that performance on the WCST, Category Fluency, and IQ all loaded on the same dimension in their group of schizophrenic patients. Thus, the working memory measures used in this study may have measured general level of intellectual functioning as opposed to working memory as specifically defined in the animal literature where there is no mention of general intelligence. Indeed, Baddeley (1990) described working memory as a process fundamental to complex abilities such as learning and language.

The question that is raised is whether the tasks we used actually measured the (working memory) functions of area 46 that we aimed to measure. Although the SDRT task has been validated in animal lesion studies, it is unclear how well it generalizes to humans. Area 46 may be involved in more complex cognitive processes in humans than in monkeys. In turn, working memory may be more complex in humans than it is in monkeys. Human cognition differs from monkeys in that they have more available cognitive resources such as language and higher level reasoning than monkeys. Humans may recruit these functions during working memory performance while monkeys rely on more specific functions simply because others are not available to them. Humans may not only recruit more complex cognitive processes than animals while performing working memory tasks, they also may use working memory processes to perform higher order cognitive functions. Working memory is considered one of the highest forms of cognitive functioning in monkeys, while humans exhibit far more complex cognitive abilities. Goldman-Rakic (1992), Baddeley (1990) and others consider working memory to be fundamental to language comprehension, learning, and reason in human beings.

The inconsistencies between human and animal working memory are apparent in the way different researchers define working memory and in the tasks they choose to measure working memory performance. In the animal literature, prototypical working memory tasks (e.g. SDRT) require retention of information over a short period of time until a response is made. Working memory tasks are distinguished from associative memory tasks in that they require responses that are based on internal representations of recently acquired information as opposed to being guided by external cues from the environment (Goldman-Rakic, 1992). Working memory in humans may be more complex. Goldman-Rakic (1992) describes working memory in humans as complementing "associative memory by providing for the short-term storage of symbolic information, as well as by permitting the manipulation of that information." It is the second part of this description that suggests that working memory may be different in humans compared to monkeys. In humans, manipulation of information in short term memory seems to be central to working memory, which is not the case with animals. In the present study, the spatial delayed response task did not require manipulation of information, it required storing information over a delay with distraction. If manipulation of information is the critical aspect of area 46 functioning in humans, the SDRT task would not be an appropriate measure. On the other hand, the SOP task clearly required manipulation and constant updating of information in short term memory. Performance on this task also was not associated with area 46 volumes. It will be important for future research to seek to further clarify these issues. What are the critical aspects of working memory performance in humans? Is distraction during the delay period comparable to having to actively manipulate the to-be remembered material over the delay period. Do humans recruit other cognitive functions to aid their working memory performance? If so, what are the factors that dictate what cognitive abilities are used? Can we isolate a specific cognitive process that relies primarily on are 46 functioning in humans?

Volumetric MRI Measures

In the present study we used volumetric MRI analysis to identify neural pathology in schizophrenia. It is believed that differences in the volumes of brain structures may grossly reflect various types of pathology such as abnormal loss of brain tissue, underdevelopment of brain structures, overgrowth of cells and neural connections, abnormal pruning, or other processes that may affect brain volumes. An additional assumption is that the volumes of brain structures are related to the functioning of those structures. Although some studies have shown relationships between the size of certain brain structures and cognitive functioning (Seidman et al., 1994), others have failed to find such relationships (Andreasen et al., 1986). One of the problems with structural MRI measures is that there are no simple, inexpensive, or non-invasive way to validate them. Although recent advances in functional imaging provide the theoretical possibility of validating structural measures, it has not been used for this purpose. Therefore, an alternative approach has been to validate MRI measures by identifying behavioral correlates.

The volumetric measures of area 46, used in the present study had not previously been validated and the only behavioral correlate of area 46, as measured in the present study, was a weak association with quantitative handedness among schizophrenics. It is possible that our measures simply did not capture the cytoarchitecturally defined area 46 region. The definition of area 46 used in the present study was based on a cytoarchitectural study of the left hemispheres of five postmortem human brains (Rajkowska & Goldman-Rakic, 1994). Given the extensive intra-individual variability of brain structures, and gyral patterns in particular, Rajkowska and Goldman-Rakic's sample may not have been representative of the population at large. It also is possible that the region defined for this series of left hemispheres does not generalize to the right hemisphere. Moreover, if schizophrenia is indeed a brain disease, it may not be appropriate to apply guidelines developed for defining brain regions in normal individuals to the brains of schizophrenic patients. Even if Rajkowska and Goldman-Rakic's (1994) definition of area 46 does generalize across hemispheres and individuals, measuring this region on MRI remains a difficult task. In the present study, only the middle portion of the region defined by these investigators was measured because the borders of the anterior and posterior middle frontal gyrus were unclear and could not be measured reliably. Measuring the middle portion of this region also was difficult and required a rigid rule system that may have sacrificed validity for the sake of reliability.

The problem of validating volumetric MRI measures is a difficult to resolve. Currently, there are no standard, well validated, protocols for measuring specific brain structures. Cortical regions are particularly problematic because of the lack of clear morphological boundaries. In terms of measuring area 46, 3D surface rendering may guide identification of sulcal landmarks that border the middle frontal gyrus. Functional magnetic resonance imaging will also be useful in this regard as it provides information about regional brain functions along with structural landmarks

SUMMARY AND FUTURE DIRECTIONS

In summary, one primary hypotheses -- that negative symptoms are specifically associated with working memory dysfunction, was weakly supported. A stronger finding was that negative symptoms were related to lower levels of cognitive functioning in general. The findings that positive and disorganized symptoms were not as strongly related to cognitive impairments suggest relative specificity in this association. This raises questions regarding the differential patterns of cognitive deficits displayed by patients with negative, positive, and disorganized symptoms of schizophrenia. Positive and disorganized symptoms may be related to more specific regional brain dysfunction while negative symptoms may involve diffuse brain dysfunction or impairment of multiple brain systems influencing a wide range of cognitive functions. Other brain regions that have been implicated in internal generation of responses and motor response selection include anterior cingulate cortex, anterior medial frontal cortex, the thalamus, the striatum, and the globus pallidus (Heilman & Watson, 1991; Passingham, 1993). It is possible that damage to these regions or connected structures lead to negative symptoms. The medial prefrontal region, in particular has been implicated in internal generation of responses and would be a worthwhile region to explore with regard to negative symptomatology.

It is possible that the hypothesis that DLPFC pathology leads to negative symptoms is correct, but that the measures used were not specific to DLPFC functioning. It will be important to continue to assess the validity of using experimental cognitive measures and tasks borrowed from animal research for evaluation of regional brain functioning in human subjects. We can not assume that, by using tasks that have been well established in the animal literature, that humans are using the same cognitive processes to solve the task. Continued research will be necessary to identify tasks that are functionally specific in humans and/or to delineate the nature of the relationship between working memory and general cognition.

Hypotheses regarding structural MRI findings were not strongly supported. Area 46_c volumes alone were not predictive of negative symptomatology and also were not associated with performance on working memory measures. On the other hand, right area 46_c volume, when considered with IQ performance in a regression, was a significant predictor of negative symptoms. Further investigations are needed to clarify the relationships between area 46, cognitive functioning, and negative symptoms. This will require further methodological investigations to validate volumetric measures of this region. Three dimensional surface rendering may aid in identification of cortical landmarks and analysis of tissue densities may reveal more subtle neuronal changes that may not be detected in gross volumetric measures. Functional magnetic resonance imaging studies could help to identify dysfunction of brain systems and also validate the use of certain cognitive measures to assess regional brain functions.

As a single group, schizophrenic patients were impaired on a variety of cognitive tasks regardless of symptomatology. The findings regarding differential associations between various cognitive measures and symptoms clusters suggest that schizophrenia is not a homogeneous disorder. Nonetheless, it is possible that there are some core cognitive deficits that are common to all schizophrenic individuals and that an overlay of additional cognitive deficits is associated with certain symptoms. Furthermore, previous research suggests that not all of the cognitive deficits in schizophrenia remain stable over time, that some cognitive functions improve as positive symptoms remit. Therefore, identification of any core cognitive deficits common to all schizophrenics will require longitudinal studies that consider patterns of symptoms and fluctuation over time.

Schizophrenia is an extremely complex disorder that is studied by investigators from numerous disciplines. Different groups of researchers are searching for influences from genetic factors, neurotransmitter systems, cellular pathology, perinatal environment, viruses, cognitive dysfunction, psychosocial variables, and other contributing factors. Ultimately, it will be necessary to integrate these different approaches in our research. It is likely that schizophrenia results from a complex set of circumstances and interactions that may not be revealed unless we consider a variety of vantage points. These factors likely combine in different ways to produce the variety of symptom patterns that are manifest in patients with schizophrenia. It will be necessary to continue to explore these interactions through multidisciplinary research that will reveal the influences of different combinations of variables.

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APPENDIX A

DSM IV DEFINITIONS OF SYMPTOMS AND SUBTYPES OF SCHIZOPHRENIA

Table A 1

Descriptions of DSM IV symptoms of schizophrenia

---

1 Delusions are false beliefs Simple persecutory delusions are beliefs that are plausible but not likely such as when the person believes that certain strangers are planning to harm him or her Bizarre delusions are those that would be regarded as totally implausible such as the belief that one's thoughts are being broadcast to the world, or that one is being controlled by a dead person

2. Hallucinations are disorders of perception Auditory hallucinations are the most common and frequently involve falsely hearing voices coming from outside one's head The voices may be familiar and often make insulting remarks or command the individual to do something Tactile and/or visual hallucinations are occasionally present. Less common are olfactory or gustatory hallucinations.

3 Disorganized speech (formal thought disorder) is a disturbance in the manner in which thoughts are expressed to others The most common form of thought disorder is looseness of associations, in which ideas shift from one subject to a completely new or only tangentially related subject, without the speaker displaying awareness that the topics are unconnected When this is severe the person's speech may become incomprehensible Another disturbance of thought is poverty of content of speech, which refers to speech that is adequate in amount, but conveys little information.

4 Grossly disorganized behavior refers to a variety of inappropriate or non-goal directed behaviors. For example the person may be inappropriately silly may display inappropriate sexual behaviors (e.g public masturbation) may appear markedly disheveled, and must have significant problems performing daily activities.

5 Catatonic behavior typically involves abnormal posturing, resistance or cessation of motor responses. The DSM-IV describes 5 types of catatonia catatonic stupor, a decrease in reactivity to the environment; catatonic rigidity maintenance of a rigid posture catatonic negativism, active resistance to instructions or attempts to be moved, catatonic posturing, the assumption of inappropriate or bizarre posturing catatonic excitement, purposeless or excessive motor activity

6 Negative symptoms refer to a diminution or loss of normal functioning in certain areas. While DSM IV describes at least five negative symptoms, only three are included in the definition of schizophrenia. Affective flattening is a diminished range of emotional expression, poor eye contact, and reduced body language Alogia or poverty of speech refers to minimal verbal responding, decreased spontaneous speech, and diminished fluency Avolition is manifest by diminished interest and drive as well as the inability to initiate and follow through with goal directed activity

Table A 2

DSM IV Features Associated with Schizophrenia, but Not Central to its Definition.

1. Inappropriate affect is expression of emotion that is not congruent with the content of speech and/or the situation. The DSM-III-R also includes the abnormal experience of emotion, such as "having no feelings" or sudden bursts of anger, as disturbances of affect.

2. A disturbance of sense of self is evidenced by extreme confusion about one's identity, loss of self directedness, and lack of recognition of one's own personal boundaries or those of other.

3. Anhedonia is a loss of interest or pleasure in activities, things, or people.

4. Psychomotor poverty is a decrease in reactivity to the environment with a reduction in spontaneous movements and activity that is not severe enough to be considered catatonic.

Table A 3

DSM-IV Subtypes of Schizophrenia

1. Catatonic Type. This type is marked by psychomotor disturbance in the form of catatonic rigidity, posturing, stupor, negativism, or [illegible] motor excitement.

2. Disorganized Type. The essential features are incoherence, loosening of associations, and disturbed affect.

3. Paranoid Type. This type involves preoccupation with one or more delusions and/or frequent auditory hallucinations related to a single theme.

4. Undifferentiated Type. Prominent psychotic symptoms are present, but either can not be classified or meet the criteria for more than one type.

5. Residual Type. This category is used when the person has had at least one episode of psychosis, but is currently without prominent psychotic features. However, they may still show signs of illness, such as social withdrawal or blunted affect.

APPENDIX B

METHOD FOR MEASURING THE MIDDLE FRONTAL GYRUS

The middle frontal gyrus (MFG) lies between the inferior frontal sulcus (IFS) and the superior frontal sulcus (SFS). Measuring the MFG requires accurate identification of these two sulci. The following instructions allow reliable identification of these sulci.

Inferior Frontal Sulcus

Locate the anteriormost image containing the genu of the corpus callosum. The IFS is usually horizontal at this level (see Figure B-1).

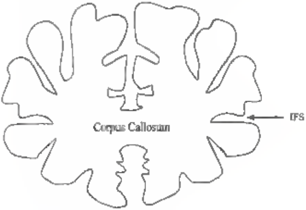


Figure B-1. Example of a horizontal inferior frontal sulcus

In cases where there are two possible sulci, choose the one that remains most prominent as you page anteriorly through the images. If the IFS disappears as you page anteriorly, choose the sulcus closest to Talairach coordinate 0 (Tal 0) in the horizontal plane (see Figure B-2). The IFS may occassionally appear ventral to Tal 0. If no sulcus is evident, simply stop at Tal 0.

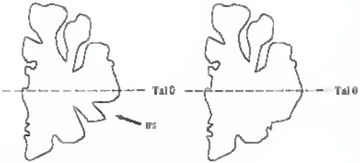


Figure B-2. Example of ventral and absent inferior frontal sulci

Superior Frontal Sulcus

The SFS is often the most prominent, or deepest, sulcus on the superior part of the prefrontal lobe (Ono et al. 1990.). The medial frontal sulcus (MdFS) is usually present and medial to this sulcus (see Figure B-3). The MdFS is often discontinuous and, therefore, may not be evident on every section. Because of this variability, it may be difficult to distinguish the SFS from the MdFS. The most accurate identification will be made by paging through the sections to identify when the MdFS is present and when it is not. Sometimes no MdFS will be present. In order to make the distinction between MdFS and SFS always choose a sulcus that is within 30 Talairach units of the midline for the SFS (see Figure B-3). If there is no such sulcus, choose the next closest one. If most of the sulcus is within 30 Talairach units, and only the top of the gyrus is outside of that region, consider the sulcus SFS.

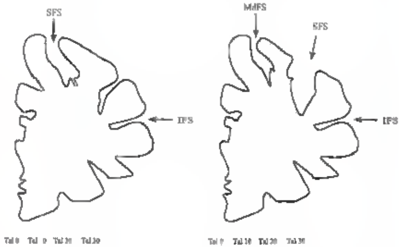


Figure B-3. Differentiating superior frontal sulcus from the medial frontal sulcus

General Rules of Measuring MFG

Merging tissue. Sometimes a sulcus that was prominent initially disappears as you move anteriorly as if two gyri fused together. In such cases chose the closest sulcus that is at least 5 Talairach units deep (see Figure B-4)

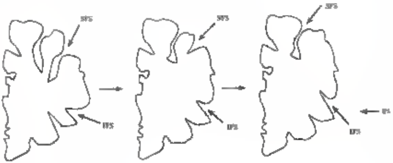
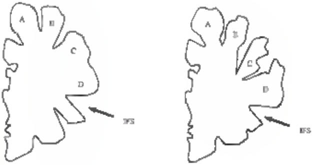


Figure B-4. Merging gyri

Gyrus split. If the MFG begins as one gyrus. Anteriorly it sometimes becomes two gyri. In such cases, continue using the outer sulcus as the boundary (see Figure B-5)

Invagination. Sometimes a "hole" will appear in the gyrus. The borders of this "hole" contain grey matter and thus need to be included in the tracing. Trace along the border of the white matter so that the grey matter is included in the encircled area (see Figure B-6)


A
B
C
D
IFS
A
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IFS

Figure B 5 . Gyrus split

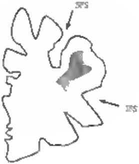


Figure B-6. Invagination of gyrus

APPENDIX C

TABLES AND GRAPHS DESCRIBING NONSIGNIFICANT FINDINGS

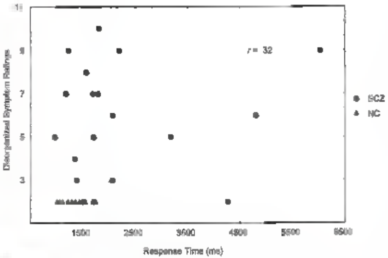


Figure C-1. Memory SDRT response times (ms) vs. disorganized symptom severity

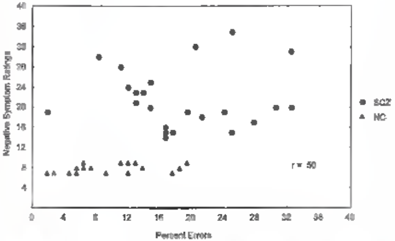


Figure G-2. Mean nonverbal SOP percent errors vs. negative symptom severity

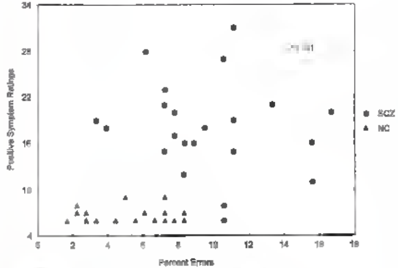


Figure G-3. Mean verbal SOP percent errors vs. positive symptom severity

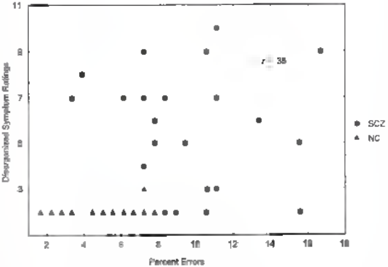
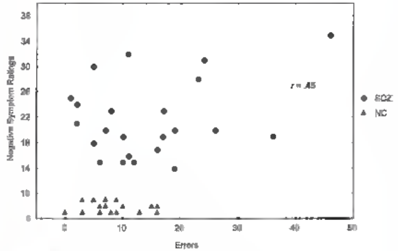


Figure C-4. Mean verbal SOP percent errors vs. disorganized symptom severity



<ins>Figure C.5.</ins> Phonemic discrimination errors vs. negative symptom severity

Table C-1

Pearson r Correlations Between Demographic Variables and Symptom Clusters

	Symptoms							
	Negative		Positive		Disorganized		General Psychopathology	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age								
Schizophrenics	−11	74	.41	.20	50	12	30	.37
Combined	13	40	.22	16	26	10	.21	17
Quantitative handedness								
Schizophrenics	16	48	.20	39	13	.57	.44	04*
Combined	−.31	94	05	74	02	88	14	17
Parental SES								
Schizophrenics	14	53	−18	44	−14	54	03	98
Combined	09	59	−16	.33	−17	.29	−12	46
Length of illness								
Schizophrenics	−08	70	.08	72	14	.53	12	.61
Frequency of hospitalizations								
Schizophrenics	−05	73	69	003**	47	07	.49	05*

Note. * Significant at $p <$ 01 ** Significant at $p <$ 05

Table C-2

Pearson *r* Correlations between Demographic Variables and WAIS-R IQ Scores

	WAIS-R Scale					
	VIQ		PIQ		FSIQ	
Variable	*r*	*p*	*r*	*p*	*r*	*p*
			Combined Groups			
Age	-0.06	0.71	-0.17	0.27	-0.12	0.42
Quantitative handedness	0.17	0.25	0.03	0.87	-0.10	0.51
Parental SES	0.14	0.37	0.21	0.17	0.20	0.20
			Schizophrenic Patients			
Age	0.16	0.46	-0.11	0.62	0.05	0.81
Quantitative handedness	-0.04	0.85	0.05	0.84	-0.003	0.99
Parental SES	0.16	0.47	0.16	0.49	0.19	0.40
Length of illness	-0.10	0.72	-0.24	0.36	-0.20	0.44
Frequency of hospitalizations	0.25	0.33	0.02	0.94	0.16	0.55
			Controls			
Age	0.01	0.98	-0.07	0.77	-0.06	0.80
Quantitative handedness	-0.56	007*	-0.07	0.76	-0.38	0.08
Parental SES	0.15	0.52	0.29	0.19	0.26	0.24

Note. * Significant at $p < .01$

Table C-3

Pearson *r* Correlations Between Demographic Variables and SDRT Performance

	Memory SDRT error distance		Memory SDRT response time		Sensory SDRT error distance		Sensory SDRT response time	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Age								
Controls	–.28	.20	15	.51	.23	.30	17	.44
Schizophrenics	.31	14	13	54	.43	04**	13	54
Combined	15	33	15	31	01	97	03	.83
Quantitative handedness								
Controls	08	73	.31	18	09	70	22	.34
Schizophrenics	10	07	08	73	001	1 00	–08	73
Combined	06	69	06	70	05	73	01	.93
Parental SES								
Controls	.22	31	25	.27	.21	.35	13	.57
Schizophrenics	11	64	.05	80	–.20	37	58	.005*
Combined	10	51	04	78	.08	61	31	.04**
Length of illness								
Schizophrenics	.23	.37	12	64	43	09	30	15
Frequency of hospitalizations								
Schizophrenics	–.39	12	.34	17	–12	.66	–.32	.21

Note. *Significant at $p < 01$ **Significant at $p < 05$

Table C-4

Pearson *r* Correlations Between Demographic Variables and Self Ordered Pointing Errors

	Verbal		Nonverbal		Total	
Variable	*r*	*p*	*r*	*p*	*r*	*p*
			Combined Groups			
Age	39	008*	.27	07	32	03**
Quantitative handedness	11	47	08	58	10	.51
Parental SES	-.25	10	-.12	43	-.17	.25
			Schizophrenic Patients			
Age	18	41	14	51	10	46
Quantitative handedness	007	97	.09	69	06	78
Parental SES	.36	.09	09	68	-.12	.59
Length of illness	28	20	.41	06	.35	11
Frequency of hospitalizations	-15	57	-18	40	-18	.49
			Controls			
Age	.59	003*	.29	.19	.46	.03**
Quantitative handedness	49	02**	.22	31	40	06
Parental SES	-25	26	-.34	.13	.32	14

Note. *Significant at $p < 01$ **Significant at $p < 05$

Table C 5

Pearson *r* Correlations Between Demographic Variables and Phonemic Discrimination Errors

	Group					
	Combined Groups		Schizophrenic Patients		Controls	
	r	*p*	*r*	*p*	*r*	*p*
	Phonemic Discrimination Errors					
Age	09	.58	.07	75	-.05	84
Quantitative handedness	10	52	14	.55	.23	.30
Parental SES	- 07	63	08	73	- 05	82
Length of illness	—	—	16	54	—	—
Frequency of hospitalizations	—	—	- 30	24	—	—

Table C 8

Pearson *r* Correlations Between Demographic Variables and Area 46 Measures

	Area 46 Measures							
	Right		Left		Total		Asymmetry	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Combined Groups								
Age	14	38	12	48	12	45	02	89
Quantitative handedness	37	02**	04	82	26	09	38	05**
Parental SES	.04	80	26	18	13	.42	.27	.09
Height	11	52	20	23	12	47	06	78
Weight	-.18	35	08	64	07	88	.21	.28
Schizophrenic Patients								
Age	.32	14	.23	30	17	45	14	.54
Quantitative handedness	.59	003*	10	.67	45	03**	-53	009*
Parental SES	40	.06	06	80	28	37	-36	09
Height	.20	.30	24	.29	13	55	-81	97
Weight	16	.47	15	50	09	78	.30	17
Length of illness	04	89	28	.28	04	86	17	.50
Frequency of	.02	95	.21	42	.28	.27	14	.58
Controls								
Age	08	74	.01	87	10	88	07	78
Quantitative handedness	01	97	.03	90	-.03	89	-.02	93
Parental SES	.32	18	.49	03**	-.48	04**	-.20	.40
Height	-.20	47	11	68	-.004	1.00	.24	37
Weight	14	61	-09	74	01	97	03	91

Note. *Significant at $p < 01$ **Significant at $p < 05$

Table C-7

Pearson r Correlations Between Demographic Variables and Planum Temporale Measures

	Planum Temporale Measures							
	Right		Left		Total		Asymmetry	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
				Combined Groups				
Age	.26	09	08	61	-.17	28	13	40
Quantitative handedness	10	54	17	27	-.07	08	-.19	.23
Parental SES	12	45	-.31	05**	.27	08	-.03	83
Height	04	82	23	17	-.11	50	-.13	43
Weight	-.07	69	06	74	.01	96	15	37
				Schizophrenic Patients				
Age	-26	.23	-.02	94	-10	45	.25	.24
Quantitative handedness	13	57	37	09	.32	14	-.09	66
Parental SES	50	02*	-.30	07	-55	007*	.23	29
Height	17	46	-28	20	-.08	73	-.29	19
Weight	12	59	12	58	10	.49	.04	86
Length of illness	.25	33	-.22	40	.29	.26	14	58
Frequency of	10	53	07	79	05	66	-.10	70
				Controls				
Age	20	40	13	57	14	58	-03	.21
Quantitative handedness	35	13	10	67	.29	23	-30	.21
Parental SES	14	58	-.27	27	-08	74	-22	.30
Height	-.40	12	-12	65	-30	17	34	19
Weight	-.47	07	-11	70	40	12	.41	11

Note. *Significant at $p <$ 01 **Significant at $p <$ 05

Table C-8

Pearson *r* Correlations Between Demographic Variables and Hemisphere Measures

	Hemisphere Measures							
	Right		Left		Total		Assymetry	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
				Combined Groups				
Age	.03	83	.02	92	81	87	-.11	46
Quantitative handedness	03	83	16	.38	11	49	.25	11
Parental SES	-.01	93	02	89	01	97	05	72
Height	-.07	88	.04	83	-.06	74	05	78
Weight	18	35	.22	18	.20	.23	16	.33
				Schizophrenic Patients				
Age	-.24	.27	17	45	-.12	58	.37	08
Quantitative handedness	12	.57	.23	.30	18	42	.32	14
Parental SES	-.06	77	12	.60	-.09	.68	16	.46
Height	-.07	78	14	58	-.11	.68	-.19	.41
Weight	.26	.31	38	13	.33	28	14	52
Length of illness	-.15	50	.21	35	-.19	.41	.23	38
Frequency of	17	.44	22	34	.20	.38	.39	12
				Controls				
Age	.26	.27	22	.36	.25	.29	-.003	99
Quantitative handedness	18	68	10	69	02	.94	.24	.29
Parental SES	-.001	1.00	07	76	05	85	11	62
Height	-.01	98	11	68	07	81	18	.48
Weight	13	63	28	33	22	41	.23	.37

BIOGRAPHICAL SKETCH

Paula Zuffante received her bachelor's degree in 1988 from Boston College where she majored in psychology. She obtained her master's degree in 1994 from the University of Florida, where she continued training for a doctorate in clinical psychology. Ms. Zuffante's primary interests are in the areas of neuropsychology and functional neuroanatomy. Her plans are to continue to pursue her research and clinical interests as a postdoctoral fellow at Long Island Jewish Medical Center in Long Island, NY.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Christiana M. Leonard

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Psychiatry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality as a dissertation for the degree of Doctor of Philosophy

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This dissertation was submitted to the Graduate Faculty of the College of Health Professions and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy

December 1997

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